GlaxoSmithKline	Statistical Analysis Plan
Detailed Title:	A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of three production lots of the Porcine circovirus (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK Biologicals' HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a two-dose vaccination in healthy infants starting at age 6-12 weeks.
eTrack study number and Abbreviated Title	115461 (ROTA-081)
Scope:	All data pertaining to the above study. Note that this analysis plan does not cover analyses devoted to iDMC. A separate SAP is available for the iDMC analyses.
Date of Statistical Analysis Plan	Final: 30-May-2017
Co-ordinating authors:	PPD (study statistician); PPD (Stat manager)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (peer reviewer statistician), PPD (Lead statistical analyst) PPD (Lead Scientific writer) PPD (Regulatory Affair) PPD (Clinical Safety representative) PPD (Public Disclosure)
Approved by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

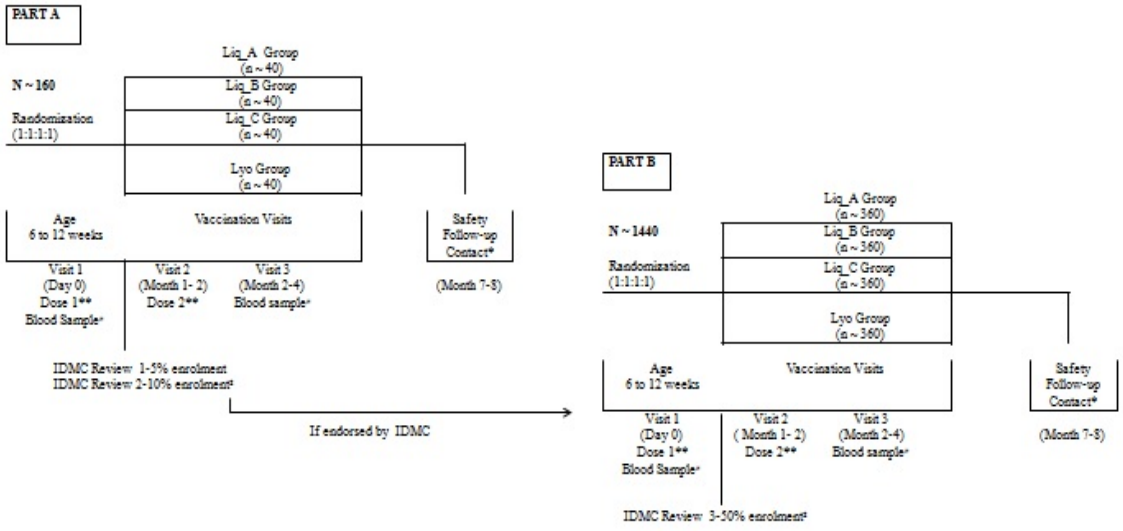
LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of Variance
cDISCI	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EL.U/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
GE	Gastroenteritis
GSK	GlaxoSmithKline
iDMC	Independent Data Monitoring Committee
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PD	Protocol Deviation
PPS	Per Protocol Set
RV	RotaVirus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
30 May 2017	first version	Amendment 1 (09March 2017)

2. STUDY DESIGN



N: Number of subjects planned to be enrolled, n = number of subjects in each group
* Contact (by telephone call or any other convenient procedure) for the safety follow-up will take place 6 months after the last dose of HRV vaccine.
** Two oral doses of the study vaccines will be administered at an approximate 1-month or 2-months interval to subjects, according to the immunisation schedule for RV vaccine administration in participating countries.
#Blood samples will be taken before the first dose and 1 to 2 months after the second dose.
$ An IDMC will review the safety data for the first 80 enrolled subjects (5% of total enrolment) and first 160 enrolled subjects (10% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available. Enrolment will be paused when first 10% of the subjects are enrolled for the purpose of the IDMC review of the safety data and will only resume if the outcome of the IDMC review is positive.
Review of the safety data for the first 800 enrolled subjects (50% of total enrolment) will be conducted as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 800 subjects.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5 of protocol), are essential and required for study conduct.

- Experimental design: Phase IIIA, observer-blind, randomised (1:1:1:1), controlled, multi-centric, with four parallel groups and a staggered enrolment (Part A and Part B).

- Duration of the study: The intended duration of the study, per subject, will be approximately 7-8 months including the 6 months of extended safety follow-up period after the last dose of HRV vaccine.
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at the safety follow-up contact (Month 7-8).
- Primary completion Date (PCD): Visit 3 (Month 2-4).

Refer to protocol glossary for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit 3 or Last Subject Last Visit (LSLV) (Follow up contact at month 7-8).

Refer to protocol glossary for the definition of EoS.

- Study groups: The study groups and epoch foreseen in the study are provided in Table 1.

Table 1 Study groups and epoch foreseen in the study

Study Groups	Number of subjects	Age at Dose 1 (Min-Max)	Epoch
			Epoch 001
Liq_A	400	6 weeks-12 weeks	●
Liq_B	400	6 weeks-12 weeks	●
Liq_C	400	6 weeks-12 weeks	●
Lyo	400	6 weeks-12 weeks	●

The study groups and treatments foreseen in the study are given in Table 2.

Table 2 Study groups and treatments foreseen in the study

Treatment name	Vaccine name	Study Groups			
		Liq_A	Liq_B	Liq_C	Lyo
HRV Liquid	HRV PCV-free ‡	x	x	x	
HRV Lyophilised	HRV *				x

‡ PCV-free HRV liquid vaccine
* Licensed formulation of HRV lyophilised vaccine

  - PCV-free HRV liquid formulation lot A (also referred to as Liq_A group)
  - PCV-free HRV liquid formulation lot B (also referred to as Liq_B group)
  - PCV-free HRV liquid formulation lot C (also referred to as Liq_C group)
  - GSK Biologicals' currently licensed lyophilised HRV formulation (also referred to as Lyo group)

- Control: active control-GSK Biologicals' currently licensed lyophilised HRV vaccine.

- Vaccination schedule: Two doses of HRV vaccine to be administered according to a 0, 1-2 month schedule according to the immunisation schedule for RV vaccine administration in participating countries.
  - Concomitant administration of routine childhood vaccines will be allowed according to local immunisation practices in each participating country.
- Treatment allocation: Randomised 1:1:1:1 using GSK Biologicals' central randomisation system on Internet (SBIR).
- Blinding: observer-blind

The blinding in the study is given in Table 3.

Table 3 Blinding of study epoch

Study Epoch	Blinding*
Epoch 001	Double-blind
Epoch 001	Observer-blind

*Double blind for the three lots of PCV-free HRV liquid vaccine and observer-blind for the liquid formulation versus the lyophilised formulation.

- Sampling schedule: Blood samples will be collected from all subjects at Visit 1 and Visit 3 to measure serum anti-RV IgA antibody concentrations using Enzyme Linked Immunosorbent Assay (ELISA).
- Recording of GE episodes: Any GE episodes occurring from Dose 1 of HRV vaccine up to Visit 3 will be recorded for all subjects in the diary card. Parents/Legally Acceptable Representative(s) (LARs) will be instructed to collect stool sample(s) if the subject develops GE during the period from Dose 1 of HRV vaccine up to Visit 3. A stool sample should be collected as soon as possible after illness begins and preferably not later than 7 days after the start of GE symptoms. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes. Refer to the protocol glossary for definitions of GE and diarrhoea.
- Recording of Solicited AEs: Solicited AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) occurring between the day of each HRV vaccine dose and the following 7 days (Day 0-Day 7) will be recorded daily using diary cards for all subjects.
- Recording of Unsolicited AEs: Unsolicited AEs occurring within 31 days (Day 0-Day 30) after each dose of HRV vaccine will be recorded using diary cards for all subjects.
- Recording of SAEs: SAEs will be recorded from Visit 1 (Day 0) up to 6 months after Dose 2 of HRV vaccine.
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)
- Safety monitoring: An IDMC comprising of clinical experts and a biostatistician, will review the safety data accrued during the study and the details of the review will be

described in an IDMC charter. The IDMC review will happen after enrolment of 5%, 10% and 50% of subjects. The IDMC review will happen at the following stages:

Review of all safety data for the first 80 enrolled subjects (5% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 80 subjects.

- any available data beyond 8 days post Dose 2 will also be reviewed.
- during this IDMC review, enrolment of subjects will continue.

Review of all safety data for the first 160 enrolled subjects (10% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for160 subjects.

- any available data beyond 8 days post Dose 2 will also be reviewed.
- until this IDMC review, enrolment of subjects will pause. Enrolment will resume only if no safety concerns are raised by IDMC.

Review of all safety data for the first 800 enrolled subjects (50% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 800 subjects.

- any available data beyond 8 days post Dose 2 will also be reviewed.
- during this IDMC review, enrolment of subjects will continue.

3. OBJECTIVES

3.1. Co-Primary

- To demonstrate the lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of immunogenicity as measured by serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Consistency will be demonstrated if, for all pairs of lots, the two-sided 95% confidence intervals (CIs) for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 are within the [0.5; 2] clinical limit interval.

- To demonstrate the immunological non-inferiority of PCV-free liquid HRV vaccine as compared to the currently licensed lyophilised HRV vaccine in terms of seroconversion rates 1-2 months after Dose 2.

Non-inferiority will be demonstrated if the lower limit of the two-sided asymptotic standardized 95% CI for the difference in seroconversion rate between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and licensed lyophilised HRV vaccine is greater than or equal to -10%.

- To demonstrate the non-inferiority of the PCV-free liquid HRV vaccine to that of the currently licensed lyophilised HRV vaccine in terms of serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and the lyophilised HRV vaccine is greater than or equal to 0.67.

3.2. Secondary

Reactogenicity and safety

- To evaluate the reactogenicity of the liquid HRV vaccine and currently licensed lyophilised HRV vaccine in terms of solicited AEs during the 8 days (Day 0-Day 7) follow-up period after each vaccination.
- To assess the safety of the study vaccines in terms of unsolicited AEs during the 31 days (Day 0-Day 30) follow-up period after each vaccination and Serious Adverse Events (SAEs) during the entire study period.

Immunogenicity

- To assess the immunogenicity of the PCV-free liquid HRV vaccine and the currently licensed lyophilised HRV vaccine, in terms of percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2.

4. ENDPOINTS

4.1. Primary

- Evaluation of immunogenicity in terms of anti-RV antibody concentrations
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in each of the HRV liquid formulation groups (Liq_A, Liq_B and Liq_C).
  - Anti-RV IgA antibody seroconversion rate* 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

*Seroconversion rate is defined as the percentage of subjects who were initially seronegative (i.e., with anti-RV IgA antibody concentration < 20 U/mL prior the first dose of HRV vaccine) and developed anti-RV IgA antibody concentration ≥ 20 U/mL at Visit 3.

4.2. Secondary

- Solicited adverse events
  - Occurrence of each general solicited symptom within the 8 days (Day 0-Day 7) follow-up period after each dose of the lyophilised and PCV-free HRV liquid vaccine
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs within 31 days (Day 0-Day 30) after any dose of HRV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events
  - Occurrence of serious adverse events from Dose 1 up to study end.
- Evaluation of immunogenicity in terms of anti-RV antibody concentrations.
  - Serum anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

5. ANALYSIS SETS

5.1. Definitions

5.1.1. Exposed Set

The ES will include all subjects with at least one study vaccine administration documented:

- a safety analysis based on the ES will include all vaccinated subjects,
- an immunogenicity analysis based on the ES will include all vaccinated subjects for whom immunogenicity data are available.

The ES analysis will be performed per treatment actually administered at dose 1.

5.1.2. Per-Protocol analysis Set of immunogenicity (PPS)

The PPS for immunogenicity will include all subjects from the ES:

- who have received all doses of study vaccine,
- for whom the HRV vaccine liquid or lyophilised formulation was administered according to protocol and subjects did not regurgitate after vaccination,
- who have not received a vaccine prohibited by the protocol up to Visit 3,
- for whom the randomisation code has not been broken
- who were seronegative for serum anti-RV IgA antibodies on the day of Dose 1
- who have not received medication prohibited by the protocol up to Visit 3 as listed in Section 6.7.2 of the study protocol,
- whose underlying medical condition was not prohibited by the protocol up to Visit 3 as listed in Section 6.8 of the study protocol,
- who comply with the vaccination schedule (Table 5 of the study protocol),
- who comply with blood sampling schedule (Table 5 of the study protocol),
- for whom immunogenicity data are available at the post-vaccination sampling time point,
- who have no RV other than vaccine strain in Gastroenteritis (GE) stool samples collected up to Visit 3,
- who have no concomitant infection unrelated to the vaccine up to Visit 3, which may influence the immune response.

5.2. Criteria for eliminating data from analyses sets

5.2.1. Elimination from Exposed set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Per-Protocol analysis Set (PPS)

A subject will be excluded from the PPS analysis under the following conditions

Code	Decode => Condition under which the code is used
900	Questionable subject => subjects with invalid informed consent or fraudulent data
1030	Study vaccine dose not administrated but subject number allocated => subjects enrolled but not vaccinated
1040	Administration of vaccine(s) forbidden in the protocol => Administration of a vaccine not foreseen by the study protocol and administered during the period starting from 30 days before the first vaccination and ending at Visit 3, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study, and other licensed routine childhood vaccinations.
1060	Randomisation code broken at the investigator site => Subjects unblinded in SBIR or unblinding reported as protocol deviation
1070	Study vaccine dose not administered according to protocol => • Subjects vaccinated with the correct vaccine but who regurgitated for one of the 2 doses; • subjects for whom the second administered dose is not aligned with the first dose (e.g. lyo as second dose after a first dose with liquid from lot A; or liquid from lot B as second dose after a first dose with liquid from lot A) • Subject who did not receive the second dose and return to visit 3 blood sample • Subject who was given multiple doses at one visit • Route of vaccination which is not oral
1080	Vaccine temperature deviation => Subjects who have received a vaccine which had a temperature deviation qualified as inappropriate for use by Quality Assurance.
1090	Expired vaccine administered => Subjects who received an expired vaccine

Code	Decode => Condition under which the code is used
2010	Protocol violation (inclusion/exclusion criteria) => Ineligible subjects who was vaccinated (i.e. Age at dose 1 is not between 42-90 days, gestational age is < 37 weeks 0 day or > 41 weeks 6 days or other eligibility criteria – see section 4.2 and 4.3 of the protocol)
2020	Initially seropositive or initially unknown antibody status = > Anti-HRV concentration ≥ 20 U/mL or unknown at pre-dose 1 blood sample
2040	Administration of any medication forbidden by the protocol => administration of • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used between Visit 1 and Visit 3 during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period between Visit 1 to Visit 3. For corticosteroids, this will mean prednisone (0.5 mg/kg/day, or equivalent). Inhaled and topical steroids are allowed. • Immunoglobulins and/or any blood products administered during the study period between Visit 1 to Visit 3. • Long-acting immune-modifying drugs administered at any time during the study period (e.g., infliximab).
2060	Concomitant infection related to the vaccine which may influence immune response => Subjects with non-vaccine type RV detected in GE stool samples that may impact immunogenicity at Visit 3.
2070	Concomitant infection not related to the vaccine which may influence immune response = > Condition that has the capability of altering their immune response at visit 3 such autoimmune disease.
2080	Non-compliance with vaccination schedule (including wrong and unknown dates) => Subjects who did not comply with the interval for dose 2 (Dose 2 should be between 28-83 days after Dose 1).
2090	Non-compliance with blood sampling schedule (including wrong and unknown dates => Subjects who did not comply with the blood sample interval (blood sample post dose 2 should be between 28-83 days after Dose 2); subjects with a blood sample at visit 3 and without a second HRV vaccine administered
2100	Essential serological data missing => Anti-HRV results not available post-vaccination
2120	Obvious incoherence or abnormality or error in data => subjects without blood sample at visit 3 for whom a sample post-vaccination is found.

5.2.3. Right censored Data

Not applicable

5.2.4. Visit-specific censored Data

Not applicable

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

The following important protocol deviations will be reported by groups:

- Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.
- Manual randomization: In case the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule. In case the randomization system is available, a vaccine different from the randomized treatment may have been administered at dose 1.
- Short follow-up: subjects with a safety follow-up period after the last dose of HRV vaccine that is less than 180 days.
- Vaccinated subjects without documentation of solicited symptoms i.e. for a vaccine dose administered, at least one solicited symptom is not documented as being present or absent.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in annex 1 and will not be repeated below. All Confidence Interval (CI) will be two-sided 95% CI.

6.1. Demography

6.1.1. Analysis of demographics/baseline characteristics planned in the protocol

The following calculations will be performed for each group and for the pooled liquid vaccine group:

- The distribution of subjects enrolled among the study centres and countries will be tabulated as a whole and for each group.
- The numbers of subjects who withdraw 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.

- The median, mean, range and standard deviation of age (in weeks) at each HRV vaccine dose and of the gestational age will be computed by group. The median, mean and standard deviation of height (in centimetres) and weight (in kilograms) at Visit 1 will be computed by group. The racial and sex composition will be presented. These calculations will also be performed by country.
- Summary of co-administered vaccinations (i.e., vaccinations given on the day of each HRV vaccine dose) and intercurrent vaccinations (i.e., vaccinations from birth up to Visit 3, excluding vaccination given on the day of HRV vaccine doses) will be summarized by group for the ES.

6.1.2. Additional considerations

All demography summaries will be generated for the ES. The summary of age, height, weight, race and sex will also be provided for the PPS. Number and reason for elimination from PPS will be tabulated by group. Summary of important protocol deviations not leading to elimination will be provided by groups for the PPS.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

Not applicable

6.2.2. Additional considerations

The number of doses administered will be tabulated for each group.

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the PPS for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.

6.3.1.1. Within groups assessment

The following calculations will be performed for each group and for the pooled liquid vaccine group.

- For each group, at each time point that anti-rotavirus IgA is measured,
  - Seropositivity/seroconversion rates and their exact 95% CI will be computed,
  - Percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL and their exact 95% CI will be computed.

  - GMCs and their 95% CIs will be computed.

- The above mentioned descriptive analyses will also be performed by country.
- The distribution of anti-RV IgA antibody concentrations at Visit 3 will be displayed using Reverse Cumulative Curves (RCCs).

6.3.1.2. Between groups assessment

- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between any pair of the three lots of the HRV liquid vaccine will be computed (first co-primary objective).
- The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine will be computed (second co-primary objective).
- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine will be computed (third co-primary objective).

6.3.1.3. Statistical Methods

- The exact CIs for a proportion within a group will be calculated using SAS [see section 11.1].
- The standardized asymptotic CI for the group difference in proportion will be calculated using SAS [see section 11.1].
- The CI for GMCs will be obtained within each group separately. The CI for the mean of log-transformed concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The CI for the GMCs will then be obtained by exponential-transformation of the CI for the mean of log-transformed concentration.
- The GMC group ratio will be obtained using an ANOVA model on the logarithm-transformed concentrations. The ANOVA model will include the vaccine group and the country as fixed effects. The GMC ratio and their 95% CI will be derived by exponential-transformation of the corresponding group contrast in the model.

6.3.2. Additional considerations

The ANOVA model for the lot-to-lot GMC ratio will include the data from the 3 HRV liquid groups only.

The country effect for the ANOVA model will be accounted by country indicator variables that will be treated as continuous variable in order to obtain adjusted GMCs that reflect the distribution of subjects between countries.

Summaries planned per countries will be limited to the PPS. These summaries will also be generated by frequent race and by gender. Note that a race category is considered if it

includes more than 40 subjects. Infrequent race categories will be combined together and summarized if it includes more than 40 subjects.

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

The ES will be used for the analysis of safety.

The following calculations will be performed for each group and for the pooled liquid vaccine group:

The percentage of doses and of subjects reporting at least one symptom (solicited or unsolicited) during the 8 days (Day 0-Day 7) solicited follow-up period post vaccination will be computed, along with exact 95% CI. The same calculations will be done for symptoms (solicited or unsolicited) rated as grade 3 in intensity and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.

The percentage of doses and of subjects reporting each individual solicited general symptom will be computed, over the 8 days (Day 0-Day 7) solicited follow-up period post vaccination, along with exact 95% CI. The same calculations will be done for each individual general solicited symptom rated as grade 3 in intensity, for each individual solicited general symptom assessed as causally related to vaccination and those that resulted in a medically attended visit.

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 days (Day 0-Day 30) 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, for unsolicited AEs with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of subjects reporting GE episodes from Dose 1 of HRV vaccine up to Visit 3 will be tabulated by group.

The percentage of subjects with presence of RV in GE stool samples collected from Dose 1 of HRV vaccine up to Visit 3 will be tabulated by group.

The percentage of GE episodes with no available stool results from Dose 1 of HRV vaccine up to Visit 3 will be tabulated.

The percentage of subjects who started taking at least one concomitant medication from HRV vaccination to Day 7 after vaccinations will be tabulated with exact 95% CI. The percentages of subjects who started taking at least one concomitant medication during the study period will be tabulated with exact 95% CI.

SAEs reported during the study period will be described in detail.

6.4.2. Additional considerations

As indicated in section 10.5 of the protocol and in line with the project history, analysis of safety will be primarily performed per dose administered and subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). A sensitivity analysis will be performed on documented doses i.e. accounting only for doses where solicited symptoms are indicated as being absent/present in case more than 5% of the doses are not documented.

Summary of temperature will be provided by 0.5° increment (i.e. ≥ 38.0°C, >38.5; > 39, > 39.5, > 40).

Summary of solicited symptoms will also be provided by country, gender and frequent race(s) while summary of unsolicited symptoms within 31 days post-vaccination will be provided by country – see section 6.3.2 for the definition of frequent race.

Summary of solicited symptoms will also be provided for each individual general solicited symptom causally related to vaccination and rated as grade 3 in intensity. Likewise the percentage of subjects and of doses with grade 3 causally related unsolicited AEs occurring within 31 days (Day 0-Day 30) follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. These summaries will not be provided by country, gender or frequent race(s).

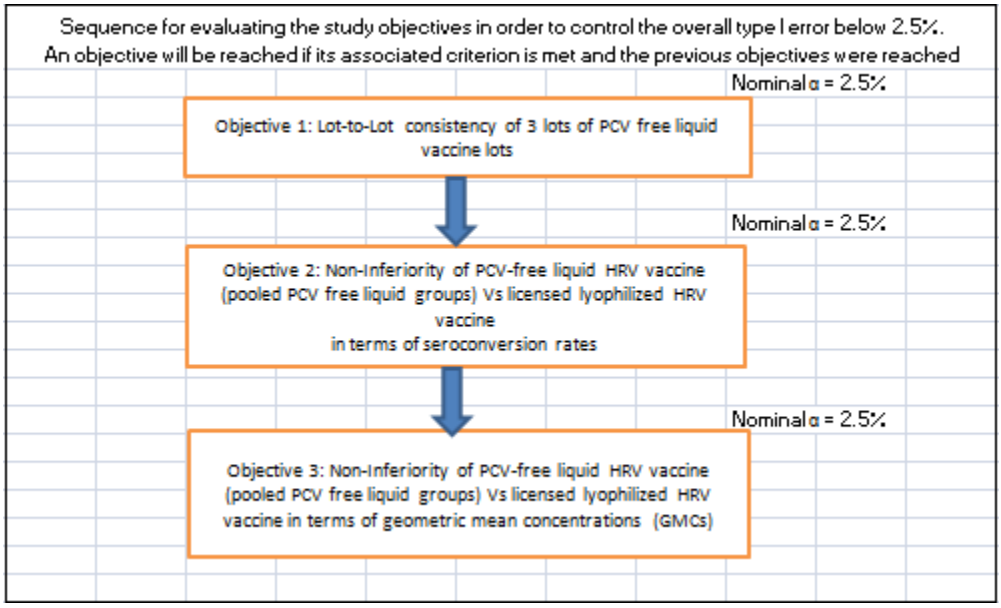
Note that the study will be converted in cDISC. Accordingly Day 0-Day 7 and Day 0-Day 30 will be replaced by Day 1-Day 8 and Day 1-Day 31 for the statistical analysis.

7. ANALYSIS INTERPRETATION

Except for analyses addressing criteria specified in the co-primary objectives referred as confirmatory analyses, all the analyses will be descriptive/exploratory in nature. The use of these descriptive/exploratory analyses should be limited to support the confirmatory analyses or to generate hypothesis.

To control the overall type I error below 2.5%, the confirmatory objectives will be evaluated using a hierarchical procedure as shown in Figure 1. A confirmatory objective will be reached if the associated criteria are met and the previous objectives have been met.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%



8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Safety data that is as clean as possible will be analysed for IDMC review. Details of the review are described in an IDMC charter.

8.1.1. Final analysis up to Visit 3:

An analysis will be conducted once all the study data up to Visit 3 are available and cleaned and Rota-IgA ELISA testing at 1-2 month post-dose 2 has been fully completed. The Clinical Study Report (CSR) with data up to Visit 3 will be used for the registration of PCV-free liquid vaccine in European Union (EU) and 'rest of world' countries.

The study report will include the following:

- All analysis of the serum anti-RV IgA antibody concentrations, 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
- All analyses of safety up to visit 3 and analysis of SAEs and AEs leading to drop out based on the database lock for the analysis.

8.2. Final analysis

If the previous analysis does not cover all study data, the study report will be amended when all data will be available. The study report amendment will include the additional safety information

The following table provides the plan for analyses excluding analyses dedicated to IDMC

Description	Analysis ID	Disclosure Purpose (IN=internal, CTRS=public posting, SR=study report and public posting)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis up to Visit 3	E1_05	SR	Yes	Yes	TFL TOC first version – All TFLs as per database lock date
Final	E1_01	SR	No	Yes	TFL TOC first version - All TFLs

8.3. Statistical considerations for interim analyses

All confirmatory analyses will be conducted for the Final analysis up to Visit 3 and therefore no statistical adjustment for interim analyses is required.

9. CHANGES FROM PLANNED ANALYSES

Not applicable

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The mock tables referred under column named ‘layout’ can be found in Annex 3 of this SAP.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
1	Liq_A	PCV-free HRV liquid vaccine - lot A
2	Liq_B	PCV-free HRV liquid vaccine - lot B
3	Liq_C	PCV-free HRV liquid vaccine - lot C
4	Liq pooled	PCV-free HRV liquid vaccine - Pooled Lot
5	Lyo	HRV Lyophilised vaccine

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413.The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med.* 1998; 17, 873-890. The standardised asymptotic method used is the method six.

11.1.1. Date derivation

- SAS date derived from a character date: in case day is missing, PPD is used. In case day & month are missing, PPD is used.
- Onset day for an event (ae, medication, vaccination, …): the onset day is the number of days between the last study vaccination & the onset/start date of the event. This is 1 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.

11.1.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 1 refers to all vaccines administered at the first vaccination visit while dose 2 corresponds to all vaccinations administered at the second vaccination visit even if this is the first time a product is administered to the subject.

- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered and an event occurs after the subsequent study dose (e.g. 2nd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g. dose 2).
- The number of doses for a product is the number of time the product was administered to a subject.
- The incidence per dose is the number of vaccination visits at which an event was reported among all vaccination visits.

11.1.3. Demography

Age: Age at the reference activity, computed as the number of complete weeks between the date of birth and the reference activity.

Conversion of weight to kg: the following conversion rule is used:

Weight in Kilogram= weight in Pounds / 2.2

Weight in Kilogram =weight in ounces / 35.2

The result is rounded to 2 decimals.

Conversion of height to cm: the following conversion rule is used:

Height in Centimetres = Height in Feet * 30.48

Height in Centimetres = Height in Inch * 2.54

The result is rounded to the unit (i.e. no decimal).

Conversion of temperature to °C: the following conversion rule is used:

Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

The result is rounded to 1 decimal.

11.1.4. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.
- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3 of the protocol.

- A seronegative subject is a subject whose antibody concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody concentration is greater than or equal to the cut-off value of the assay.
- The assay cut-off is the value under which there is no quantifiable result available. For an assay with a specific 'cut_off' , numerical immuno result is derived from a character field (rawres):
  - If rawres is 'NEG' or '-' or '(-)', numeric result= cut_off/2,
  - if rawres is 'POS' or '+' or '(+)', numeric result = cut_off,
  - if rawres is '< value' and value<=cut_off, numeric result =cut_off/2,
  - if rawres is '< value' and value>cut_off, numeric result =value,
  - if rawres is '> value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '> value' and value>=cut_off, numeric result =value,
  - if rawres is '<= value' or '>= value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '<= value' or '>= value' and value>=cut_off, numeric result =value,
  - if rawres is a value < cut_off, numeric result = cut_off/2,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - else numeric result is left blank.

11.1.5. Safety

- For analysis of solicited, unsolicited adverse events (such as serious adverse events or adverse events by primary MedDRA term) and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- In case there will be more than 5% of subjects without documented dose for solicited symptoms (i.e., symptom screen not completed), sensitivity analysis will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed).
- The following rules will be used for the analysis of solicited symptoms:
  - Subject who didn't document the presence or absence of a solicited symptom after one dose will be considered not having that symptom after that dose in the analysis done on "administrated dose"
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
  - Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.

– Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be considered as having that symptom after that dose).

- For the analysis, temperatures will be coded as follows for oral, axillary or tympanic route:

Grade	Temperature
0	< 38.0°C
1	≥ 38.0°C - ≤ 38.5°C
2	> 38.5°C - ≤ 39.5°C
3	> 39.5°C

- Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	**N used for deriving % per subject for Vaccination phase**	**N used for deriving % per dose for Vaccination phase**
Concomitant vaccination	All subjects with study vaccine administered	All study visits with study vaccine administered
Solicited general symptom	Primary analysis: all subjects with study vaccine administered Sensitivity analysis as applicable (see section 6.4.2): all subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	Primary analysis: all study visits with study vaccine administered Sensitivity analysis: all study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered
Concomitant medication	All subjects with study vaccine administered	All study visits with study vaccine administered

For summaries by MedDRA primary preferred term combining solicited and unsolicited adverse events, solicited adverse events will be coded as per the following MedDRA codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Fever	10016558	Fever
Irritability/Fussiness	10022998	Irritability
Diarrhoea	10012727	Diarrhoea
Vomiting	10047700	Vomiting
Loss of appetite	10003028	Appetite lost
Cough/runny nose	10011224	Cough

11.1.6. Management of missing data

Demography:

- For a given subject and a given demographic variable, missing measurements will not be replaced.

Immunogenicity:

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

Reactogenicity and safety:

- Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

11.1.7. Data presentation description

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
Demographic characteristics	Mean, median, SD	1
Immunogenicity	% of difference, including LL & UL of CI	2
Immunogenicity	GMC group ratio, including LL & UL of CI	2
Immunogenicity	Anti-RV IgA GMC	1

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to Section 5.2.

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used.

The data display, title and footnote are for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC.

These templates were copied from ROTA-061 and additional tables required for public disclosure were added. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs. These editorial/minor changes will not lead to a SAP amendment.

Note that all tables will include the pooled lot group for HRV liquid as shown in Template 2.

Template 1 Minimum and maximum activity dates (Exposed Set)

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

*Database Lock Date = 31MAR2009

Template 2 Number of subjects enrolled by center - Exposed Set

Country	Center	LIQ_A	LIQ_B	LIQ_C	LIQ_pool	LYO	Total	
		n	n	n	n	n	n	%
XXXX	PPD	38	38	38		37	151	12.6
	PPD	20	20	20		20	80	6.7
	PPD	30	30	29		29	118	9.8
	PPD	19	19	20		20	78	6.5
	All							
YYYYY	PPD	15	15	15		15	60	5.0
	PPD	22	22	23		22	89	7.4
	PPD	35	36	36		35	142	11.8
	PPD	28	28	28		28	112	9.3
	PPD	20	21	20		21	82	6.8
	PPD	22	23	22		23	90	7.5
	PPD	22	23	22		23	90	7.5
	PPD	27	27	27		27	108	9.0
	All							
All	All	298	302	300		300	1200	100

<group description >
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

Template 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal entire study period- Exposed Set

	LIQ_A	LIQ_B	LIQ_C	LYO	Total
Number of subjects vaccinated	298	302	300	300	1200
Number of subjects completed	297	301	298	297	1193
Number of subjects withdrawn	1	1	2	3	7
Reasons for withdrawal :					
Serious Adverse Event	0	0	0	1	1
Non-serious adverse event	0	0	0	0	0
Protocol violation	0	0	0	0	0
Consent withdrawal (not due to an adverse event)	1	0	1	2	4
Migrated/moved from study area	0	1	1	0	2
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	0	0	0	0
Others	0	0	0	0	0

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed study visit 3
Withdrawn = number of subjects who did not come for study visit 3

Template 4 Number of subjects at each visit and list of withdrawn subjects (Exposed Set)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
Liq_A	VISIT 1	508		
			no. PP	CONSENT WITHDRAWAL
			no. PP	CONSENT WITHDRAWAL
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	CONSENT WITHDRAWAL
	VISIT 2	504		
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	SERIOUS ADVERSE EXPERIENCE
	VISIT 3	501		
			no. P	MIGRATION FROM STUDY AREA
			no. PP	CONSENT WITHDRAWAL
			no. PP	MIGRATION FROM STUDY AREA
			no. PP	CONSENT WITHDRAWAL
			no. PPD	MIGRATION FROM STUDY AREA
			no. PP	MIGRATION FROM STUDY AREA
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	MIGRATION FROM STUDY AREA
			no. PPD	MIGRATION FROM STUDY AREA
	VISIT 4	492		
Lyo	VISIT 1	257		
			no. PP	PROTOCOL VIOLATION
			no. PPD	CONSENT WITHDRAWAL
	VISIT 2	255		
			no. PPD	CONSENT WITHDRAWAL
	VISIT 3	254		
			no. PP	MIGRATION FROM STUDY AREA
			no. PP	LOST TO FOLLOW-UP
			no. PP	LOST TO FOLLOW-UP
			no. PP	CONSENT WITHDRAWAL
			no. PP	MIGRATION FROM STUDY AREA
			no. PPD	LOST TO FOLLOW-UP
			no. PPD	ADVERSE EXPERIENCE
	VISIT 4	247		

Template 5 Number of subjects enrolled into the study as well as the number of subjects excluded from PPS analyses with reasons for exclusion

	Total				LIQ_A			LIQ_B			LIQ_C			LYO		
Title	**N**	**n**	**s**	**%**	**N**	**n**	**s**	**N**	**n**	**s**	**N**	**n**	**s**	**N**	**n**	**s**
Total enrolled cohort	**1200**				**298**			**302**			**300**			**300**		
Exposed Set	**1200**			**100**	**298**			**302**			**300**			**300**		
Administration of vaccine(s) forbidden in the protocol (code 1040)		2	2			1	1		1	1		0	0		0	0
Study vaccine dose not administered according to protocol (code 1070)		73	73			21	21		13	13		23	23		16	16
Initially seropositive or unknown anti-rotavirus IgA antibody on day of dose 1 (code 1500)		10	11			3	4		3	3		3	3		1	1
Protocol violation (inclusion/exclusion criteria) (code 2010)		1	1			0	0		0	0		1	1		0	0
Administration of any medication forbidden by the protocol (code 2040)		1	1			0	0		0	0		0	0		1	1
Underlying medical condition forbidden by the protocol (code 2050)		1	1			1	1		0	0		0	0		0	0
Concomitant infection not related to the vaccine which may influence immune response (code 2070)		0	1			0	0		0	0		0	0		0	1
Non-compliance with vaccination schedule (including wrong and unknown dates) (code 2080)		14	16			5	5		0	0		6	7		3	4
Non-compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)		12	16			2	3		3	3		3	5		4	5
Essential serological data missing (code 2100)		87	95			23	25		21	22		20	22		23	26
Subjects with incomplete study vaccination schedule but with post serological result (code 2500)		1	1			0	0		1	1		0	0		0	0
Per protocol set	**998**			**83.2**	**242**			**260**			**244**			**252**		

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LYO = HRV vaccine lyophilised formulation
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 per protocol set (PPS) relative to the exposed set (ES)

Template 6 Summary of demographic characteristics (Per Protocol Analysis Set of Immunogenicity)

		LIQ_A N = 242		LIQ_B N = 260		LIQ_C N = 244		LYO N = 252		Total N = 998	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 of HRV vaccine (weeks)	Mean	11.6	-	11.5	-	11.5	-	11.6	-	11.6	-
	SD	1.32	-	1.16	-	1.19	-	1.20	-	1.22	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	10	-	10	-	10	-	10	-	10	-
	Maximum	17	-	15	-	15	-	16	-	17	-
Age at Dose 2 of HRV vaccine (weeks)	Mean	16.6	-	16.5	-	16.5	-	16.7	-	16.6	-
	SD	1.48	-	1.40	-	1.37	-	1.34	-	1.40	-
	Median	17.0	-	16.0	-	16.0	-	17.0	-	17.0	-
	Minimum	14	-	14	-	14	-	14	-	14	-
	Maximum	22	-	20	-	20	-	21	-	22	-
Gender	Female	122	50.4	121	46.5	120	49.2	120	47.6	483	48.4
	Male	120	49.6	139	53.5	124	50.8	132	52.4	515	51.6
Ethnicity	American Hispanic or Latino	0	0.0	2	0.8	1	0.4	0	0.0	3	0.3
	Not American Hispanic or Latino	242	100.0	258	99.2	243	99.6	252	100.0	995	99.7
Race	African heritage / African American	1	0.4	0	0.0	1	0.4	0	0.0	2	0.2
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - central/south Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - south east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / north African heritage	0	0.0	0	0.0	2	0.8	0	0.0	2	0.2
	White - Caucasian / European heritage	239	98.8	258	99.2	240	98.4	247	98.0	984	98.6
	Other	2	0.8	2	0.8	1	0.4	5	2.0	10	1.0
Height at Visit 1 (cm)	Mean	60.4	-	60.5	-	60.7	-	60.6	-	60.5	-
	SD	2.35	-	2.37	-	2.32	-	2.22	-	2.32	-
	Median	61.0	-	60.0	-	61.0	-	61.0	-	61.0	-
	Unknown	0	-	1	-	2	-	0	-	3	-
Weight at Visit 1 (kg)	Mean	6.0	-	6.1	-	6.2	-	6.1	-	6.1	-
	SD	0.77	-	0.76	-	0.77	-	0.75	-	0.76	-
	Median	6.0	-	6.0	-	6.2	-	6.1	-	6.1	-
BMI at Visit 1 (kg/m^2)	Mean	16.5	-	16.6	-	16.7	-	16.7	-	16.6	-
	SD	1.49	-	1.46	-	1.46	-	1.46	-	1.47	-
	Median	16.3	-	16.5	-	16.5	-	16.7	-	16.5	-
	Unknown	0	-	1	-	2	-	0	-	3	-

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
N = total number of subjects
n (%) = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Template 7 Deviations from specifications for age and intervals between study visits - Exposed Set

		Age	PRE-Dose:1	Dose:1-Dose:2		Dose:2-PII(M2)	
Group		**Protocol**	**Protocol**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
		from 10 to 17 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**
LIQ_A	**N**	298	298	297	297	287	287
	n	0	2	8	7	1	1
	%	0.0	0.7	2.7	2.4	0.3	0.3
	range	10 to 17	0 to 4	29 to 76	29 to 76	30 to 55	30 to 55
LIQ_B	**N**	302	302	301	301	294	294
	n	0	1	0	0	4	2
	%	0.0	0.3	0.0	0.0	1.4	0.7
	range	10 to 15	0 to 3	30 to 48	30 to 48	24 to 56	24 to 56
LIQ_C	**N**	300	300	300	300	291	291
	n	1	1	8	7	4	4
	%	0.3	0.3	2.7	2.3	1.4	1.4
	range	9 to 17	0 to 9	27 to 76	27 to 76	30 to 56	30 to 56
LYO	**N**	300	300	299	299	289	289
	n	0	2	4	4	5	3
	%	0.0	0.7	1.3	1.3	1.7	1.0
	range	10 to 16	0 to 3	30 to 61	30 to 61	28 to 61	28 to 61

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
PRE = pre-vaccination
PII (M2) = blood sample taken one month after Dose 2 of the HRV vaccine (Visit 3)
Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals

Template 8 Summary of co-administered vaccination by dose - Exposed Set

Dose1	LIQ_A N = 298		LIQ_B N = 302		LIQ_C N = 300		LYO N = 300		Total N = 1200	
Characteristics	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Any	298	100	302	100	299	99.7	300	100	1199	99.9
Infanrix hexa	298	100	302	100	299	99.7	300	100	1199	99.9
Dose 2	**LIQ_A N = 297**		**LIQ_B N = 301**		**LIQ_C N = 300**		**LYO N = 299**		**Total N = 1197**	
Characteristics	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Any	297	100	301	100	298	99.3	299	100	1195	99.8
Infanrix hexa	297	100	301	100	298	99.3	299	100	1195	99.8

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
N = total number of subjects having received the considered dose of HRV
n/% = number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV vaccine

Template 9 Summary of vaccinations other than HRV vaccine administered from birth until Visit 3, excluding vaccination given on the day of HRV doses - Exposed Set

Before Dose 1	LIQ_A N = 298			LIQ_B N = 302			LIQ_C N = 300			LYO N = 300			Total N = 1200		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	18	18	6.0	11	11	3.6	13	13	4.3	25	25	8.3	67	67	5.6
BCG	18	18	6.0	11	11	3.6	12	12	4.0	25	25	8.3	66	66	5.5
Infanrix hexa™	0	0	0.0	0	0	0.0	1	1	0.3	0	0	0.0	1	1	0.1
Between Dose 1 and Dose 2§	**LIQ_A N = 298**			**LIQ_B N = 302**			**LIQ_C N = 300**			**LYO N = 300**			**Total N = 1200**		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	0	0	0.0	2	1	0.3	0	0	0.0	0	0	0.0	2	1	0.1
Infanrix hexa™	0	0	0.0	2	1	0.3	0	0	0.0	0	0	0.0	2	1	0.1
Between Dose 2 and Visit 3*	**LIQ_A N = 297**			**LIQ_B N = 301**			**LIQ_C N = 300**			**LYO N = 299**			**Total N = 1197**		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	291	291	98.0	295	295	98.0	287	286	95.3	290	290	97.0	1163	1162	97.1
DTPa+IPV+Hib	0	0	0.0	1	1	0.3	0	0	0.0	0	0	0.0	1	1	0.1
Infanrix hexa™	291	291	98.0	294	294	97.7	287	286	95.3	290	290	97.0	1162	1161	97.0

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
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
§= up to last contact of conclusion at Visit 3 if dose 2 of HRV was not administered
*= up to last contact of conclusion at Visit 3 if visit 3 was not done

Template 10 Anti-rotavirus IgA antibody GMC and seroconversion rates – Per Protocol Analysis Set of Immunogenicity

			≥ 20 U/ml				GMC (U/ml)		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
LIQ_A	PRE	242	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	242	220	90.9	86.6	94.2	384.4	309.1	478.2
LIQ_B	PRE	260	0	0.0	0.0	1.4	<20	-	-
	PII(M2)	260	235	90.4	86.1	93.7	418.8	337.8	519.1
LIQ_C	PRE	244	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	244	206	84.4	79.3	88.7	324.4	253.4	415.3
LIQPOOL	PRE	746	0	0.0	0.0	0.5	<20	-	-
	PII(M2)	746	661	88.6	86.1	90.8	374.7	328.8	426.9
LYO	PRE	252	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	252	228	90.5	86.2	93.8	331.8	265.0	415.4

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects with available results
n (%) = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L =Lower limit; U.L = upper limit
Pre = pre-vaccination
PII (M2) = blood sample taken one month after Dose 2 of HRV vaccine (Visit 3)

Template 11 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies – Per Protocol Analysis Set of Immunogenicity

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
LIQ_A	PII(M2)	220	553.8	463.4	661.7
LIQ_B	PII(M2)	235	623.0	525.0	739.4
LIQ_C	PII(M2)	206	616.4	510.4	744.4
LIQPOOL	PII(M2)	661	597.1	538.7	661.8
LYO	PII(M2)	228	479.7	395.4	582.0

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; LL = Lower Limit; UL = Upper Limit
PII(M2) = blood sample taken one month after Dose 2 of HRV vaccine (Visit 3)

Template 12 Ratio of anti-rotavirus IgA antibody GMCs 1-2 months after Dose 2 of the HRV vaccine between each pair of the three lots of the HRV PCV-free liquid vaccine – Per Protocol Analysis Set of Immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
LIQ_A	242	384.4	**LIQ_B**	260	418.8	**LIQ_A /LIQ_B**	0.92	0.67*	1.26*
LIQ_A	242	384.4	**LIQ_C**	244	324.4	**LIQ_A /LIQ_C**	1.19	0.86*	1.64*
LIQ_B	260	418.8	**LIQ_C**	244	324.4	**LIQ_B /LIQ_C**	1.29	0.94*	1.77*

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects with available results
95% CI = 95% Confidence Interval (one-way ANOVA model with pooled variance from the four groups)
L.L. = Lower Limit, U.L. = Upper Limit
*The two-sided 95% CIs are within [0.5; 2] (the pre-defined clinical limit interval for consistency)

Template 13 Difference between groups in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody 1-2 months after Dose 2 of the HRV vaccine – Per Protocol Analysis Set of Immunogenicity

						Difference in seroconversion rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
LIQPOOL	746	88.6	**LYO**	252	90.5	**LYO - LIQPOOL**	1.87	-2.85	5.83*

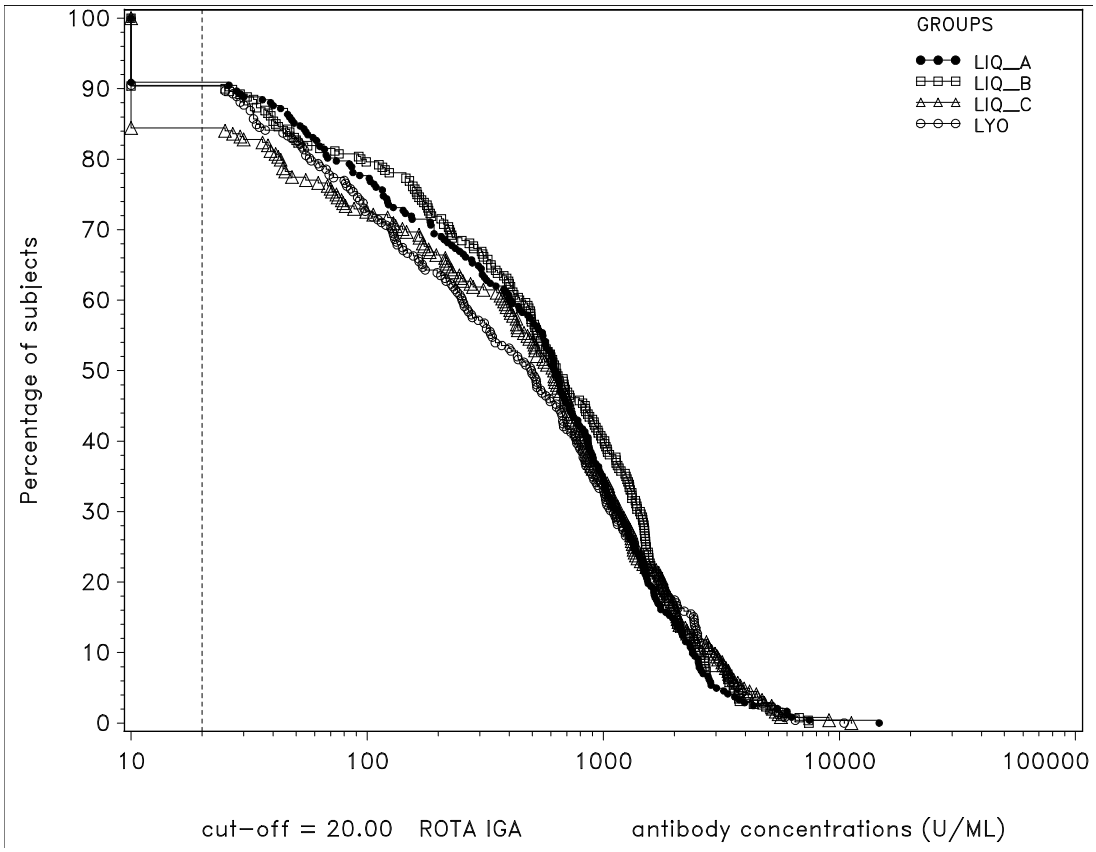
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects with available results
% = percentage of subjects who seroconverted at visit 3
95% CI = asymptotic standardised 95% Confidence Interval; LL = Lower Limit; UL = Upper Limit
*Lower limit of the 95% CI ≥-10% (the pre-defined clinical limit for non-inferiority)

Template 14 Ratio of anti-rotavirus IgA antibody GMCs 1-2 months after Dose 2 of the HRV vaccine between the HRV lyophilised vaccine group and the pooled HRV PCV-free liquid vaccine – Per Protocol Analysis Set of Immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
LIQPOOL	746	373.8†	LYO	252	331.8	LYO /LIQPOOL	0.89	0.68	1.15*

LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects with available results
†geometric mean of the 3 GMC from the HRV liquid formulation groups
95% CI = 95% Confidence Interval (one-way ANOVA model using the group contrast between the HRV lyophilised formulation group and average of the HRV liquid formulation groups)
L.L. = Lower Limit, U.L. = Upper Limit
*Lower limit of the 95% CI ≥ 0.67 (the pre-defined clinical limit for non-inferiority)

Template 15 Reverse cumulative distribution curve for anti-rotavirus IgA antibody concentrations at Visit 3 - Per Protocol Analysis Set of Immunogenicity



Template 16 Number and percentage of subjects who received study vaccine doses - Exposed Set

	LIQ_A N = 298		LIQ_B N = 302		LIQ_C N = 300		LYO N = 300		Total N = 1200	
Total number of doses received	n	%	n	%	n	%	n	%	n	%
1	1	0.3	1	0.3	0	0.0	1	0.3	3	0.3
2	297	99.7	301	99.7	300	100	299	99.7	1197	99.8
Any	298	100	302	100	300	100	300	100	1200	100

LIQ_A = HRV vaccine Liquid formulation lot A LIQ_B = HRV vaccine Liquid formulation lot B
LIQ_C = HRV vaccine Liquid formulation lot C LYO = HRV vaccine lyophilised formulation
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

Template 17 Compliance in returning symptom sheets - Exposed Set

Dose	GROUP	Number of doses	Doses NOT according to protocol	Number of general SS	Compliance % general SS
1	LIQ_A	298	10	298	100
	LIQ_B	302	7	302	100
	LIQ_C	300	6	300	100
	LIQPOOL	900	23	900	100
	LYO	300	6	299	99.7
2	LIQ_A	297	12	296	99.7
	LIQ_B	301	6	301	100
	LIQ_C	300	13	299	99.7
	LIQPOOL	898	31	896	99.8
	LYO	299	9	297	99.3
Total	LIQ_A	595	22	594	99.8
	LIQ_B	603	13	603	100
	LIQ_C	600	19	599	99.8
	LIQPOOL	1798	54	1796	99.9
	LYO	599	15	596	99.5

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
SS = Symptom sheets used for the collection of solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100
Doses not according to protocol = number of doses with regurgitation or vomiting

Template 18 Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) reported during the 8-day (Day 0 to Day 7) follow-up period - Exposed Set

		Any symptom				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	LIQ_A	298	251	84.2	79.6	88.2
	LIQ_B	302	267	88.4	84.3	91.8
	LIQ_C	300	247	82.3	77.5	86.5
	LIQPOOL	900	765	85.0	82.5	87.3
	LYO	300	249	83.0	78.3	87.1
Dose 2	LIQ_A	297	247	83.2	78.4	87.2
	LIQ_B	301	260	86.4	82.0	90.0
	LIQ_C	300	236	78.7	73.6	83.2
	LIQPOOL	898	743	82.7	80.1	85.2
	LYO	299	247	82.6	77.8	86.7
Overall/dose	LIQ_A	595	498	83.7	80.5	86.6
	LIQ_B	603	527	87.4	84.5	89.9
	LIQ_C	600	483	80.5	77.1	83.6
	LIQPOOL	1798	1508	83.9	82.1	85.5
	LYO	599	496	82.8	79.5	85.7
Overall/subject	LIQ_A	298	283	95.0	91.8	97.2
	LIQ_B	302	287	95.0	91.9	97.2
	LIQ_C	300	275	91.7	87.9	94.5
	LIQPOOL	900	845	93.9	92.1	95.4
	LYO	300	279	93.0	89.5	95.6

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
For each dose:
N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by at least one symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 19 Percentage of subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, after each dose of the HRV lyophilised and HRV PCV-free liquid vaccine for all groups. - Exposed Set

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Cough/runny nose	All	298	72	24.2	19.4	29.4	302	90	29.8	24.7	35.3	300	71	23.7	19.0	28.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	62	20.8	16.3	25.9	302	76	25.2	20.4	30.5	300	49	16.3	12.3	21.0
Diarrhoea	All	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
	Grade 3	298	3	1.0	0.2	2.9	302	2	0.7	0.1	2.4	300	2	0.7	0.1	2.4
	Related	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
Fever(°C)	All	298	63	21.1	16.6	26.2	302	59	19.5	15.2	24.5	300	57	19.0	14.7	23.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	61	20.5	16.0	25.5	302	58	19.2	14.9	24.1	300	55	18.3	14.1	23.2
Irritability	All	298	213	71.5	66.0	76.5	302	225	74.5	69.2	79.3	300	191	63.7	57.9	69.1
	Grade 3	298	12	4.0	2.1	6.9	302	17	5.6	3.3	8.9	300	9	3.0	1.4	5.6
	Related	298	203	68.1	62.5	73.4	302	220	72.8	67.5	77.8	300	184	61.3	55.6	66.9
Loss of appetite	All	298	79	26.5	21.6	31.9	302	79	26.2	21.3	31.5	300	73	24.3	19.6	29.6
	Grade 3	298	0	0.0	0.0	1.2	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	75	25.2	20.3	30.5	302	78	25.8	21.0	31.2	300	67	22.3	17.7	27.5
Vomiting	All	298	47	15.8	11.8	20.4	302	45	14.9	11.1	19.4	300	44	14.7	10.9	19.2
	Grade 3	298	11	3.7	1.9	6.5	302	7	2.3	0.9	4.7	300	7	2.3	0.9	4.7
	Related	298	45	15.1	11.2	19.7	302	43	14.2	10.5	18.7	300	39	13.0	9.4	17.3
Dose 2																
Cough/runny nose	All	297	92	31.0	25.8	36.6	301	104	34.6	29.2	40.2	300	95	31.7	26.4	37.3
	Grade 3	297	2	0.7	0.1	2.4	301	2	0.7	0.1	2.4	300	4	1.3	0.4	3.4
	Related	297	79	26.6	21.7	32.0	301	84	27.9	22.9	33.3	300	79	26.3	21.4	31.7
Diarrhoea	All	297	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	300	12	4.0	2.1	6.9
	Grade 3	297	1	0.3	0.0	1.9	301	2	0.7	0.1	2.4	300	2	0.7	0.1	2.4
	Related	297	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	300	12	4.0	2.1	6.9
Fever(°C)	All	297	80	26.9	22.0	32.4	301	79	26.2	21.4	31.6	300	94	31.3	26.1	36.9
	Grade 3	297	2	0.7	0.1	2.4	301	1	0.3	0.0	1.8	300	1	0.3	0.0	1.8
	Related	297	79	26.6	21.7	32.0	301	76	25.2	20.4	30.6	300	91	30.3	25.2	35.9
Irritability	All	297	201	67.7	62.0	73.0	301	224	74.4	69.1	79.3	300	202	67.3	61.7	72.6
	Grade 3	297	11	3.7	1.9	6.5	301	18	6.0	3.6	9.3	300	14	4.7	2.6	7.7
	Related	297	195	65.7	60.0	71.0	301	220	73.1	67.7	78.0	300	200	66.7	61.0	72.0
Loss of appetite	All	297	69	23.2	18.5	28.5	301	63	20.9	16.5	26.0	300	70	23.3	18.7	28.5
	Grade 3	297	1	0.3	0.0	1.9	301	0	0.0	0.0	1.2	300	0	0.0	0.0	1.2

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
	Related	297	67	22.6	17.9	27.7	301	59	19.6	15.3	24.5	300	68	22.7	18.1	27.8
Vomiting	All	297	43	14.5	10.7	19.0	301	40	13.3	9.7	17.7	300	33	11.0	7.7	15.1
	Grade 3	297	7	2.4	1.0	4.8	301	8	2.7	1.2	5.2	300	8	2.7	1.2	5.2
	Related	297	40	13.5	9.8	17.9	301	40	13.3	9.7	17.7	300	32	10.7	7.4	14.7

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 20 Percentage of subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, for each dose in the pooled HRV PCV-free liquid vaccine group and the HRV vaccine lyophilised formulation group - Exposed Set

		LIQPOOL					LYO				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/runny nose	All	900	233	25.9	23.1	28.9	300	79	26.3	21.4	31.7
	Grade 3	900	2	0.2	0.0	0.8	300	4	1.3	0.4	3.4
	Related	900	187	20.8	18.2	23.6	300	64	21.3	16.8	26.4
Diarrhoea	All	900	25	2.8	1.8	4.1	300	4	1.3	0.4	3.4
	Grade 3	900	7	0.8	0.3	1.6	300	1	0.3	0.0	1.8
	Related	900	25	2.8	1.8	4.1	300	3	1.0	0.2	2.9
Fever(°C)	All	900	179	19.9	17.3	22.6	300	68	22.7	18.1	27.8
	Grade 3	900	2	0.2	0.0	0.8	300	0	0.0	0.0	1.2
	Related	900	174	19.3	16.8	22.1	300	67	22.3	17.7	27.5
Irritability	All	900	629	69.9	66.8	72.9	300	207	69.0	63.4	74.2
	Grade 3	900	38	4.2	3.0	5.7	300	12	4.0	2.1	6.9
	Related	900	607	67.4	64.3	70.5	300	201	67.0	61.4	72.3
Loss of appetite	All	900	231	25.7	22.8	28.7	300	67	22.3	17.7	27.5
	Grade 3	900	1	0.1	0.0	0.6	300	1	0.3	0.0	1.8
	Related	900	220	24.4	21.7	27.4	300	63	21.0	16.5	26.1
Vomiting	All	900	136	15.1	12.8	17.6	300	55	18.3	14.1	23.2
	Grade 3	900	25	2.8	1.8	4.1	300	11	3.7	1.8	6.5
	Related	900	127	14.1	11.9	16.6	300	51	17.0	12.9	21.7
Dose 2											
Cough/runny nose	All	898	291	32.4	29.4	35.6	299	109	36.5	31.0	42.2
	Grade 3	898	8	0.9	0.4	1.7	299	2	0.7	0.1	2.4
	Related	898	242	26.9	24.1	30.0	299	89	29.8	24.6	35.3
Diarrhoea	All	898	22	2.4	1.5	3.7	299	8	2.7	1.2	5.2
	Grade 3	898	5	0.6	0.2	1.3	299	3	1.0	0.2	2.9
	Related	898	22	2.4	1.5	3.7	299	8	2.7	1.2	5.2
Fever(°C)	All	898	253	28.2	25.3	31.2	299	74	24.7	20.0	30.0
	Grade 3	898	4	0.4	0.1	1.1	299	3	1.0	0.2	2.9
	Related	898	246	27.4	24.5	30.4	299	71	23.7	19.0	29.0
Irritability	All	898	627	69.8	66.7	72.8	299	200	66.9	61.2	72.2
	Grade 3	898	43	4.8	3.5	6.4	299	12	4.0	2.1	6.9
	Related	898	615	68.5	65.3	71.5	299	196	65.6	59.9	70.9
Loss of appetite	All	898	202	22.5	19.8	25.4	299	62	20.7	16.3	25.8
	Grade 3	898	1	0.1	0.0	0.6	299	0	0.0	0.0	1.2
	Related	898	194	21.6	19.0	24.4	299	60	20.1	15.7	25.1
Vomiting	All	898	116	12.9	10.8	15.3	299	41	13.7	10.0	18.1
	Grade 3	898	23	2.6	1.6	3.8	299	11	3.7	1.9	6.5
	Related	898	112	12.5	10.4	14.8	299	40	13.4	9.7	17.8

LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 21 Percentage of doses and subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, after each dose of the HRV lyophilised and HRV PCV-free HRV liquid vaccine for all groups. - Exposed Set

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose																
Cough/runny nose	All	595	164	27.6	24.0	31.3	603	194	32.2	28.5	36.1	600	166	27.7	24.1	31.4
	Grade 3	595	3	0.5	0.1	1.5	603	2	0.3	0.0	1.2	600	5	0.8	0.3	1.9
	Related	595	141	23.7	20.3	27.3	603	160	26.5	23.0	30.3	600	128	21.3	18.1	24.8
Diarrhoea	All	595	11	1.8	0.9	3.3	603	16	2.7	1.5	4.3	600	20	3.3	2.0	5.1
	Grade 3	595	4	0.7	0.2	1.7	603	4	0.7	0.2	1.7	600	4	0.7	0.2	1.7
	Related	595	11	1.8	0.9	3.3	603	16	2.7	1.5	4.3	600	20	3.3	2.0	5.1
Fever(°C)	All	595	143	24.0	20.7	27.7	603	138	22.9	19.6	26.4	600	151	25.2	21.7	28.8
	Grade 3	595	3	0.5	0.1	1.5	603	1	0.2	0.0	0.9	600	2	0.3	0.0	1.2
	Related	595	140	23.5	20.2	27.1	603	134	22.2	19.0	25.8	600	146	24.3	21.0	28.0
Irritability	All	595	414	69.6	65.7	73.3	603	449	74.5	70.8	77.9	600	393	65.5	61.5	69.3
	Grade 3	595	23	3.9	2.5	5.7	603	35	5.8	4.1	8.0	600	23	3.8	2.4	5.7
	Related	595	398	66.9	62.9	70.7	603	440	73.0	69.2	76.5	600	384	64.0	60.0	67.8
Loss of appetite	All	595	148	24.9	21.4	28.6	603	142	23.5	20.2	27.1	600	143	23.8	20.5	27.4
	Grade 3	595	1	0.2	0.0	0.9	603	0	0.0	0.0	0.6	600	1	0.2	0.0	0.9
	Related	595	142	23.9	20.5	27.5	603	137	22.7	19.4	26.3	600	135	22.5	19.2	26.1
Vomiting	All	595	90	15.1	12.3	18.3	603	85	14.1	11.4	17.1	600	77	12.8	10.3	15.8
	Grade 3	595	18	3.0	1.8	4.7	603	15	2.5	1.4	4.1	600	15	2.5	1.4	4.1
	Related	595	85	14.3	11.6	17.4	603	83	13.8	11.1	16.8	600	71	11.8	9.4	14.7
Overall/subject																
Cough/runny nose	All	298	134	45.0	39.2	50.8	302	147	48.7	42.9	54.5	300	132	44.0	38.3	49.8
	Grade 3	298	3	1.0	0.2	2.9	302	2	0.7	0.1	2.4	300	5	1.7	0.5	3.8
	Related	298	118	39.6	34.0	45.4	302	125	41.4	35.8	47.2	300	108	36.0	30.6	41.7
Diarrhoea	All	298	11	3.7	1.9	6.5	302	15	5.0	2.8	8.1	300	19	6.3	3.9	9.7
	Grade 3	298	4	1.3	0.4	3.4	302	4	1.3	0.4	3.4	300	3	1.0	0.2	2.9
	Related	298	11	3.7	1.9	6.5	302	15	5.0	2.8	8.1	300	19	6.3	3.9	9.7
Fever(°C)	All	298	111	37.2	31.7	43.0	302	104	34.4	29.1	40.1	300	122	40.7	35.1	46.5
	Grade 3	298	3	1.0	0.2	2.9	302	1	0.3	0.0	1.8	300	2	0.7	0.1	2.4
	Related	298	109	36.6	31.1	42.3	302	100	33.1	27.8	38.7	300	118	39.3	33.8	45.1
Irritability	All	298	254	85.2	80.7	89.1	302	267	88.4	84.3	91.8	300	240	80.0	75.0	84.4
	Grade 3	298	20	6.7	4.1	10.2	302	31	10.3	7.1	14.3	300	21	7.0	4.4	10.5
	Related	298	252	84.6	80.0	88.5	302	265	87.7	83.5	91.2	300	238	79.3	74.3	83.8
Loss of appetite	All	298	111	37.2	31.7	43.0	302	113	37.4	31.9	43.1	300	111	37.0	31.5	42.7
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	106	35.6	30.1	41.3	302	108	35.8	30.4	41.5	300	109	36.3	30.9	42.1
Vomiting	All	298	70	23.5	18.8	28.7	302	59	19.5	15.2	24.5	300	61	20.3	15.9	25.3
	Grade 3	298	18	6.0	3.6	9.4	302	12	4.0	2.1	6.8	300	12	4.0	2.1	6.9
	Related	298	69	23.2	18.5	28.4	302	58	19.2	14.9	24.1	300	58	19.3	15.0	24.3

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by the specified symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the specified symptom
All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 22 Percentage of subjects with unsolicited symptoms classified by MedDRA SOC and PT from Day 0 to Day 30 after any vaccination in each HRV PCV-free vaccine liquid group - Exposed Set

Primary System Organ Class (CODE)	Preferred Term (CODE)	LIQ_A N = 298				LIQ_B N = 302				LIQ_C N = 300			
				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		24	8.1	5.2	11.7	26	8.6	5.7	12.4	33	11.0	7.7	15.1
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	1	0.3	0.0	1.8
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	1.2	2	0.7	0.1	2.4	1	0.3	0.0	1.8
	Flatulence (10016766)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	2	0.7	0.1	2.4
General disorders and administration site conditions (10018065)	Injection site erythema (10022061)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Injection site pain (10022086)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Injection site swelling (10053425)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Irritability (10022998)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	1	0.3	0.0	1.8
	Pyrexia (10037660)	4	1.3	0.4	3.4	3	1.0	0.2	2.9	4	1.3	0.4	3.4
Immune system disorders (10021428)	Hypersensitivity (10020751)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
Infections and infestations (10021881)	Bronchitis (10006451)	2	0.7	0.1	2.4	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Ear infection (10014011)	1	0.3	0.0	1.9	3	1.0	0.2	2.9	2	0.7	0.1	2.4
	Exanthema subitum (10015586)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Eye infection (10015929)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Gastroenteritis (10017888)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Impetigo (10021531)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Influenza (10022000)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Laryngitis (10023874)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Otitis media (10033078)	5	1.7	0.5	3.9	6	2.0	0.7	4.3	11	3.7	1.8	6.5
	Perianal abscess (10034447)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2

Primary System Organ Class (CODE)	Preferred Term (CODE)	LIQ_A N = 298				LIQ_B N = 302				LIQ_C N = 300			
				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pneumonia (10035664)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Respiratory tract infection (10062352)	3	1.0	0.2	2.9	2	0.7	0.1	2.4	0	0.0	0.0	1.2
	Respiratory tract infection viral (10062106)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rhinitis (10039083)	2	0.7	0.1	2.4	1	0.3	0.0	1.8	3	1.0	0.2	2.9
	Upper respiratory tract infection (10046306)	2	0.7	0.1	2.4	5	1.7	0.5	3.8	7	2.3	0.9	4.7
	Varicella (10046980)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	2	0.7	0.1	2.4
Psychiatric disorders (10037175)	Crying (10011469)	0	0.0	0.0	1.2	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	1.9	1	0.3	0.0	1.8	6	2.0	0.7	4.3
	Nasal congestion (10028735)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Rales (10037833)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Eczema (10014184)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rash (10037844)	2	0.7	0.1	2.4	0	0.0	0.0	1.2	0	0.0	0.0	1.2

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the MedDRA PT
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 23 Percentage of doses with unsolicited symptoms classified by MedDRA SOC and PT from Day 0 to Day 30 after vaccination in each HRV PCV-free liquid vaccine group - Exposed Set

		LIQ_A N = 595				LIQ_B N = 603				LIQ_C N = 600			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		25	4.2	2.7	6.1	30	5.0	3.4	7.0	38	6.3	4.5	8.6
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	1	0.2	0.0	0.9
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	0.6	2	0.3	0.0	1.2	1	0.2	0.0	0.9
	Flatulence (10016766)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	2	0.3	0.0	1.2
General disorders and administration site conditions (10018065)	Injection site erythema (10022061)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Injection site pain (10022086)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Injection site swelling (10053425)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Irritability (10022998)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.2	0.0	0.9
	Pyrexia (10037660)	4	0.7	0.2	1.7	3	0.5	0.1	1.4	4	0.7	0.2	1.7
Immune system disorders (10021428)	Hypersensitivity (10020751)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Infections and infestations (10021881)	Bronchitis (10006451)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Ear infection (10014011)	1	0.2	0.0	0.9	3	0.5	0.1	1.4	2	0.3	0.0	1.2
	Exanthema subitum (10015586)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Eye infection (10015929)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Gastroenteritis (10017888)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Impetigo (10021531)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Influenza (10022000)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Laryngitis (10023874)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Otitis media (10033078)	6	1.0	0.4	2.2	7	1.2	0.5	2.4	12	2.0	1.0	3.5
	Perianal abscess (10034447)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Pneumonia (10035664)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Respiratory tract infection (10062352)	3	0.5	0.1	1.5	2	0.3	0.0	1.2	0	0.0	0.0	0.6
	Respiratory tract infection viral (10062106)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Rhinitis (10039083)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.5	0.1	1.5
	Upper respiratory tract infection (10046306)	2	0.3	0.0	1.2	6	1.0	0.4	2.2	8	1.3	0.6	2.6
	Varicella (10046980)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	2	0.3	0.0	1.2
Psychiatric disorders (10037175)	Crying (10011469)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
Respiratory, thoracic and mediastinal disorders	Cough (10011224)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	6	1.0	0.4	2.2

		LIQ_A N = 595				LIQ_B N = 603				LIQ_C N = 600			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
(10038738)	Nasal congestion (10028735)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Rales (10037833)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Eczema (10014184)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Rash (10037844)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	0	0.0	0.0	0.6

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = Total number of doses administered
n/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the MedDRA PT
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 24 Percentage of subjects reporting any GE episodes from Dose 1 of HRV vaccine up to Visit 3 - Exposed Set

Group	Between Dose 1 and before Dose 2					Between Dose 2 and Visit 3					Between Dose 1 and Visit 3				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
LIQ_A	298	16	5.4	3.1	8.6	297	10	3.4	1.6	6.1	298	25	8.4	5.5	12.1
LIQ_B	302	17	5.6	3.3	8.9	301	15	5.0	2.8	8.1	302	29	9.6	6.5	13.5
LIQ_C	300	17	5.7	3.3	8.9	300	18	6.0	3.6	9.3	300	33	11.0	7.7	15.1
LIQPOOL	900	50	5.6	4.2	7.3	898	43	4.8	3.5	6.4	900	87	9.7	7.8	11.8
LYO	300	8	2.7	1.2	5.2	299	15	5.0	2.8	8.1	300	22	7.3	4.7	10.9

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
Between Dose 1 and before Dose 2: N = number of subjects having received the first dose
Between Dose 2 and Visit 3: N = number of subjects having received the second dose
Between Dose 1 and Visit 3: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one gastroenteritis episode during the specified period
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 25 Percentage of subjects reporting RV (vaccine strain or wild type RV) GE episodes from Dose 1 of HRV vaccine up to Visit 3 - Exposed Set

Group	Between Dose 1 and before Dose 2					Between Dose 2 and Visit 3					Between Dose 1 and Visit 3				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
LIQ_A	298	0	0.0	0.0	1.2	297	0	0.0	0.0	1.2	298	0	0.0	0.0	1.2
LIQ_B	302	1	0.3	0.0	1.8	301	0	0.0	0.0	1.2	302	1	0.3	0.0	1.8
LIQ_C	300	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8	300	1	0.3	0.0	1.8
LIQPOOL	900	1	0.1	0.0	0.6	898	1	0.1	0.0	0.6	900	2	0.2	0.0	0.8
LYO	300	0	0.0	0.0	1.2	299	0	0.0	0.0	1.2	300	0	0.0	0.0	1.2

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
Between Dose 1 and before Dose 2: N = number of subjects having received the first dose
Between Dose 2 and Visit 3: N = number of subjects having received the second dose
Between Dose 1 and Visit 3: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one RV GE episode during the specified period
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 26 Summary of RV GE episodes reported from Dose 1 of HRV vaccine up to Visit 3 - Exposed Set

Subject no	Onset of episode	Isolated RV type
PP C	Day 3 of Dose 1	G1/P8 vaccine strain
PP D	Day 23 of Dose 2	G1/P8 vaccine strain

Template 27 Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 7 after vaccination by type in each HRV PCV-free vaccine liquid group - Exposed Set

	LIQ_A					LIQ_B					LIQ_C				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1															
Any	298	173	58.1	52.2	63.7	302	175	57.9	52.2	63.6	300	157	52.3	46.5	58.1
Any antipyretic	298	97	32.6	27.3	38.2	302	94	31.1	25.9	36.7	300	71	23.7	19.0	28.9
Prophylactic antipyretic	298	8	2.7	1.2	5.2	302	6	2.0	0.7	4.3	300	9	3.0	1.4	5.6
Any antibiotic	298	6	2.0	0.7	4.3	302	5	1.7	0.5	3.8	300	5	1.7	0.5	3.8
Dose 2															
Any	297	105	35.4	29.9	41.1	301	117	38.9	33.3	44.6	300	89	29.7	24.6	35.2
Any antipyretic	297	98	33.0	27.7	38.7	301	109	36.2	30.8	41.9	300	86	28.7	23.6	34.1
Prophylactic antipyretic	297	7	2.4	1.0	4.8	301	8	2.7	1.2	5.2	300	6	2.0	0.7	4.3
Any antibiotic	297	4	1.3	0.4	3.4	301	8	2.7	1.2	5.2	300	4	1.3	0.4	3.4
Overall/dose															
Any	595	278	46.7	42.7	50.8	603	292	48.4	44.4	52.5	600	246	41.0	37.0	45.1
Any antipyretic	595	195	32.8	29.0	36.7	603	203	33.7	29.9	37.6	600	157	26.2	22.7	29.9
Prophylactic antipyretic	595	15	2.5	1.4	4.1	603	14	2.3	1.3	3.9	600	15	2.5	1.4	4.1
Any antibiotic	595	10	1.7	0.8	3.1	603	13	2.2	1.2	3.7	600	9	1.5	0.7	2.8
Overall/subject															
Any	298	194	65.1	59.4	70.5	302	205	67.9	62.3	73.1	300	182	60.7	54.9	66.2
Any antipyretic	298	130	43.6	37.9	49.5	302	141	46.7	41.0	52.5	300	111	37.0	31.5	42.7
Prophylactic antipyretic	298	11	3.7	1.9	6.5	302	12	4.0	2.1	6.8	300	13	4.3	2.3	7.3
Any antibiotic	298	10	3.4	1.6	6.1	302	13	4.3	2.3	7.2	300	9	3.0	1.4	5.6

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
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

Template 28 Percentage of subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, for each documented dose in each HRV PCV-free liquid group - Exposed Set

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Cough/runny nose	All	298	72	24.2	19.4	29.4	302	90	29.8	24.7	35.3	300	71	23.7	19.0	28.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	62	20.8	16.3	25.9	302	76	25.2	20.4	30.5	300	49	16.3	12.3	21.0
Diarrhoea	All	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
	Grade 3	298	3	1.0	0.2	2.9	302	2	0.7	0.1	2.4	300	2	0.7	0.1	2.4
	Related	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
Fever(°C)	All	298	63	21.1	16.6	26.2	302	59	19.5	15.2	24.5	300	57	19.0	14.7	23.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	61	20.5	16.0	25.5	302	58	19.2	14.9	24.1	300	55	18.3	14.1	23.2
Irritability	All	298	213	71.5	66.0	76.5	302	225	74.5	69.2	79.3	300	191	63.7	57.9	69.1
	Grade 3	298	12	4.0	2.1	6.9	302	17	5.6	3.3	8.9	300	9	3.0	1.4	5.6
	Related	298	203	68.1	62.5	73.4	302	220	72.8	67.5	77.8	300	184	61.3	55.6	66.9
Loss of appetite	All	298	79	26.5	21.6	31.9	302	79	26.2	21.3	31.5	300	73	24.3	19.6	29.6
	Grade 3	298	0	0.0	0.0	1.2	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	75	25.2	20.3	30.5	302	78	25.8	21.0	31.2	300	67	22.3	17.7	27.5
Vomiting	All	298	47	15.8	11.8	20.4	302	45	14.9	11.1	19.4	300	44	14.7	10.9	19.2
	Grade 3	298	11	3.7	1.9	6.5	302	7	2.3	0.9	4.7	300	7	2.3	0.9	4.7
	Related	298	45	15.1	11.2	19.7	302	43	14.2	10.5	18.7	300	39	13.0	9.4	17.3
Dose 2																
Cough/runny nose	All	296	92	31.1	25.9	36.7	301	104	34.6	29.2	40.2	299	95	31.8	26.5	37.4
	Grade 3	296	2	0.7	0.1	2.4	301	2	0.7	0.1	2.4	299	4	1.3	0.4	3.4
	Related	296	79	26.7	21.7	32.1	301	84	27.9	22.9	33.3	299	79	26.4	21.5	31.8
Diarrhoea	All	296	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	299	12	4.0	2.1	6.9
	Grade 3	296	1	0.3	0.0	1.9	301	2	0.7	0.1	2.4	299	2	0.7	0.1	2.4
	Related	296	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	299	12	4.0	2.1	6.9
Fever(°C)	All	296	80	27.0	22.1	32.5	301	79	26.2	21.4	31.6	299	94	31.4	26.2	37.0
	Grade 3	296	2	0.7	0.1	2.4	301	1	0.3	0.0	1.8	299	1	0.3	0.0	1.8
	Related	296	79	26.7	21.7	32.1	301	76	25.2	20.4	30.6	299	91	30.4	25.3	36.0
Irritability	All	296	201	67.9	62.3	73.2	301	224	74.4	69.1	79.3	299	202	67.6	61.9	72.8
	Grade 3	296	11	3.7	1.9	6.6	301	18	6.0	3.6	9.3	299	14	4.7	2.6	7.7
	Related	296	195	65.9	60.2	71.3	301	220	73.1	67.7	78.0	299	200	66.9	61.2	72.2
Loss of appetite	All	296	69	23.3	18.6	28.6	301	63	20.9	16.5	26.0	299	70	23.4	18.7	28.6
	Grade 3	296	1	0.3	0.0	1.9	301	0	0.0	0.0	1.2	299	0	0.0	0.0	1.2
	Related	296	67	22.6	18.0	27.8	301	59	19.6	15.3	24.5	299	68	22.7	18.1	27.9
Vomiting	All	296	43	14.5	10.7	19.1	301	40	13.3	9.7	17.7	299	33	11.0	7.7	15.1
	Grade 3	296	7	2.4	1.0	4.8	301	8	2.7	1.2	5.2	299	8	2.7	1.2	5.2
	Related	296	40	13.5	9.8	17.9	301	40	13.3	9.7	17.7	299	32	10.7	7.4	14.8

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects with the considered documented dose
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination

Template 29 Listing of dropouts due to AEs, SAEs and solicited symptoms (Total cohort)

Study-Subject No.	Country	Gender	AE Description	SAE	Causality	Outcome	Type of discontinuation
PPD	Germany	F	SUBJECT DIED	Y		Fatal	Study at visit/contact: VISIT11 (Y5)
PPD	Germany	F	SUBJECT DIED	Y		Fatal	Study at visit/contact: VISIT11 (Y5)

Template 30 Subjects with Serious Adverse Events reported up to Visit 3 - Exposed Set

Sub. No.	Country	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
PP	US	PP	M	Kawasaki's disease	Kawasaki's disease	Infections and infestations	HO	1	12	29	N	Recovered/resolved

MA = medical attention
HO = hospitalisation
Dose = dose given prior to the start of the SAE
Day of onset = number of days since last study vaccine dose

Template 31 Number (%) of subjects with serious adverse events from Dose 1 up to study end, including number of events reported (Exposed Set)

			Gr 1 N =			Gr2 N =		
Type of Event	Primary System Organ Class	Preferred Term (CODE)	n*	n	%	n*	n	%
SAE	At least one symptom							
	<each SOC>	<each PT term>						
Related SAE	At least one symptom							
	<each SOC>	<each PT term>						
Fatal SAE	At least one symptom							
	<each SOC>	<each PT term>						
Related fatal SAE	At least one symptom							
	<each SOC>	<each PT term>						

Gr 1 = Group 1 description
Gr 2 = Group 2 description
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 32 Solicited and unsolicited symptoms experienced by at least 5 % of subjects classified by MedDRA Primary System Organ Class and Preferred Term within 31-day (Days 0-30) post-vaccination period after any dose of HRV PCV-free liquid vaccine - SAE excluded (Exposed Set)

		HPV_2D N =			MMR_DTPa N =		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
At least one symptom							
<each SOC>	<each PT term>						

HPV_2D = females aged 4-6 years who received two doses of HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
MMR_DTPa = females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 33 Number of subjects by country

	ACWY-TT N = 259	**ACWYHPV N = 259**	**HPV N = 261**	**Co-ad N = 260**	**Tdap N = 261**	**Total N = 1300**
Country	**n**	**n**	**N**	**n**	**n**	**n**
Dominican Republic	86	87	88	87	87	435
Estonia	87	86	87	87	88	435
Thailand	86	86	86	86	86	430

ACWY-TT = Subjects who received MenACWY-TT at Month 0 and Cervarix at Month 1, 2 and 7
ACWYHPV = Subjects who received MenACWY-TT and Cervarix at Month 0 and Cervarix at Month 1 and 6
HPV = Subjects who received Cervarix at Month 0, 1 and 6
Co-ad = Subjects who received MenACWY-TT, Cervarix and Boostrix at Month 0 and Cervarix at Month 1 and 6
Tdap = Subjects who received Boostrix and Cervarix at Month 0 and Cervarix at Month 1 and 6
N = number of subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories

Template 34 Number of enrolled subjects by age category (Exposed Set)

		Gr 1 N =	Gr 2 N =	Gr 3 N =	Total N =
Characteristics	**Categories**	**n**	**n**	**n**	**n**
Age category	In utero				
	Preterm newborn infants (gestational age < 37 wks)				
	Newborns (0-27 days)				
	Infants and toddlers (28 days-23 months)				
	Children (2-11 years)				
	Adolescents (12-17 years)				
	Adults (18-64 years)				
	From 65-84 years				
	85 years and over				
	Missing				

Gr 1 = Group 1 description
Gr 2 = Group 2 description
Gr 3 = Group 3 description
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories
Missing = <describe missing>

Template 35 Study population (Exposed Set)

Number of subjects	[each group]	Total
Planned, N		
Randomised, N (<Total Vaccinated Cohort>)		
Completed, n (%)		
Demographics		
N (<Total Vaccinated Cohort>)		
Females:Males		
Mean Age, <years> (SD)		
Median Age, <years> (minimum, maximum)		
<Most frequent category of race>, n (%)		
<Second most frequent category of race>, n (%)		
<Third most frequent category of race>, n (%)		

[each group] :
Short group label= long group label

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of three production lots of the Porcine circovirus (PCV)-free liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK Biologicals' HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a two-dose vaccination in healthy infants starting at age 6-12 weeks.
eTrack study number and Abbreviated Title	115461 (ROTA-081)
Scope:	All data pertaining to the above study. Note that this analysis plan does not cover analyses devoted to iDMC. A separate SAP is available for the iDMC analyses.
Date of Statistical Analysis Plan	Amendment 1 Final: 05-Feb-2018
Co-ordinating authors:	PPD (study statistician); PPD (Stat manager)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (peer reviewer statistician), PPD (Lead statistical analyst) PPD (Lead Scientific writer) PPD (Regulatory Affair) PPD (Clinical Safety representative) PPD (Public Disclosure)
Approved by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF TEMPLATES

PAGE

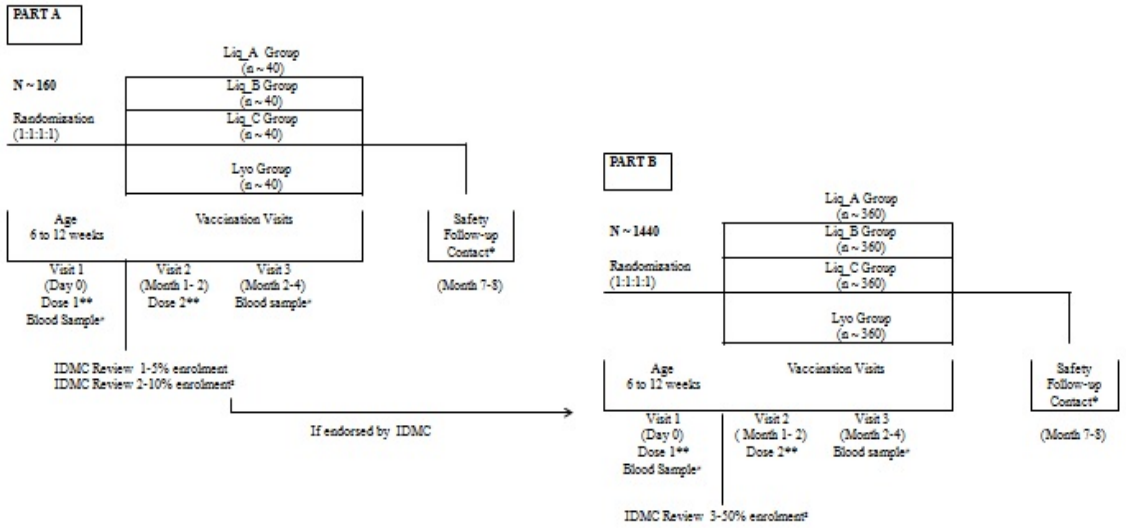
LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of Variance
cDISCI	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EL.U/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
GE	Gastroenteritis
GSK	GlaxoSmithKline
iDMC	Independent Data Monitoring Committee
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PD	Protocol Deviation
PPS	Per Protocol Set
RV	RotaVirus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
30 May 2017	first version	Amendment 1 (09March 2017)
05 Feb 2018	Amendment 1: the derivation of gastroenteritis was added in section 6.4.2.	Amendment 1 (09March 2017)

2. STUDY DESIGN



N: Number of subjects planned to be enrolled, n = number of subjects in each group

* Contact (by telephone call or any other convenient procedure) for the safety follow-up will take place 6 months after the last dose of HRV vaccine.

** Two oral doses of the study vaccines will be administered at an approximate 1-month or 2-months interval to subjects, according to the immunisation schedule for RV vaccine administration in participating countries.

#Blood samples will be taken before the first dose and 1 to 2 months after the second dose.

$ An IDMC will review the safety data for the first 80 enrolled subjects (5% of total enrolment) and first 160 enrolled subjects (10% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available. Enrolment will be paused when first 10% of the subjects are enrolled for the purpose of the IDMC review of the safety data and will only resume if the outcome of the IDMC review is positive.

Review of the safety data for the first 800 enrolled subjects (50% of total enrolment) will be conducted as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 800 subjects.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5 of protocol), are essential and required for study conduct.

- Experimental design: Phase IIIA, observer-blind, randomised (1:1:1:1), controlled, multi-centric, with four parallel groups and a staggered enrolment (Part A and Part B).
- Duration of the study: The intended duration of the study, per subject, will be approximately 7-8 months including the 6 months of extended safety follow-up period after the last dose of HRV vaccine.
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at the safety follow-up contact (Month 7-8).
- Primary completion Date (PCD): Visit 3 (Month 2-4).

Refer to protocol glossary for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit 3 or Last Subject Last Visit (LSLV) (Follow up contact at month 7-8).

Refer to protocol glossary for the definition of EoS.

- Study groups: The study groups and epoch foreseen in the study are provided in Table 1.

Table 1 Study groups and epoch foreseen in the study

Study Groups	Number of subjects	Age at Dose 1 (Min-Max)	Epoch
			Epoch 001
Liq_A	400	6 weeks-12 weeks	●
Liq_B	400	6 weeks-12 weeks	●
Liq_C	400	6 weeks-12 weeks	●
Lyo	400	6 weeks-12 weeks	●

The study groups and treatments foreseen in the study are given in Table 2.

Table 2 Study groups and treatments foreseen in the study

Treatment name	Vaccine name		Study Groups		
		Liq_A	Liq_B	Liq_C	Lyo
HRV Liquid	HRV PCV-free ‡	x	x	x	
HRV Lyophilised	HRV *				x

‡ PCV-free HRV liquid vaccine
* Licensed formulation of HRV lyophilised vaccine

  - PCV-free HRV liquid formulation lot A (also referred to as Liq_A group)
  - PCV-free HRV liquid formulation lot B (also referred to as Liq_B group)
  - PCV-free HRV liquid formulation lot C (also referred to as Liq_C group)
  - GSK Biologicals' currently licensed lyophilised HRV formulation (also referred to as Lyo group)

- Control: active control-GSK Biologicals' currently licensed lyophilised HRV vaccine.
- Vaccination schedule: Two doses of HRV vaccine to be administered according to a 0, 1-2 month schedule according to the immunisation schedule for RV vaccine administration in participating countries.
  - Concomitant administration of routine childhood vaccines will be allowed according to local immunisation practices in each participating country.
- Treatment allocation: Randomised 1:1:1:1 using GSK Biologicals' central randomisation system on Internet (SBIR).
- Blinding: observer-blind

The blinding in the study is given in Table 3.

Table 3 Blinding of study epoch

Study Epoch	Blinding*
Epoch 001	Double-blind
Epoch 001	Observer-blind

*Double blind for the three lots of PCV-free HRV liquid vaccine and observer-blind for the liquid formulation versus the lyophilised formulation.

- Sampling schedule: Blood samples will be collected from all subjects at Visit 1 and Visit 3 to measure serum anti-RV IgA antibody concentrations using Enzyme Linked Immunosorbent Assay (ELISA).
- Recording of GE episodes: Any GE episodes occurring from Dose 1 of HRV vaccine up to Visit 3 will be recorded for all subjects in the diary card. Parents/Legally Acceptable Representative(s) (LARs) will be instructed to collect stool sample(s) if the subject develops GE during the period from Dose 1 of HRV vaccine up to Visit 3. A stool sample should be collected as soon as possible after illness begins and preferably not later than 7 days after the start of GE symptoms. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes. Refer to the protocol glossary for definitions of GE and diarrhoea.
- Recording of Solicited AEs: Solicited AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) occurring between the day of each HRV vaccine dose and the following 7 days (Day 0-Day 7) will be recorded daily using diary cards for all subjects.
- Recording of Unsolicited AEs: Unsolicited AEs occurring within 31 days (Day 0-Day 30) after each dose of HRV vaccine will be recorded using diary cards for all subjects.
- Recording of SAEs: SAEs will be recorded from Visit 1 (Day 0) up to 6 months after Dose 2 of HRV vaccine.
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)

- Safety monitoring: An IDMC comprising of clinical experts and a biostatistician, will review the safety data accrued during the study and the details of the review will be described in an IDMC charter. The IDMC review will happen after enrolment of 5%, 10% and 50% of subjects. The IDMC review will happen at the following stages:

  Review of all safety data for the first 80 enrolled subjects (5% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 80 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

  – during this IDMC review, enrolment of subjects will continue.

  Review of all safety data for the first 160 enrolled subjects (10% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for160 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

  – until this IDMC review, enrolment of subjects will pause. Enrolment will resume only if no safety concerns are raised by IDMC.

  Review of all safety data for the first 800 enrolled subjects (50% of total enrolment) as soon as data until 8 days post Dose 2 (Day 0-Day 7) are available for 800 subjects.

  – any available data beyond 8 days post Dose 2 will also be reviewed.

  – during this IDMC review, enrolment of subjects will continue.

3. OBJECTIVES

3.1. Co-Primary

- To demonstrate the lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of immunogenicity as measured by serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Consistency will be demonstrated if, for all pairs of lots, the two-sided 95% confidence intervals (CIs) for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 are within the [0.5; 2] clinical limit interval.

- To demonstrate the immunological non-inferiority of PCV-free liquid HRV vaccine as compared to the currently licensed lyophilised HRV vaccine in terms of seroconversion rates 1-2 months after Dose 2.

Non-inferiority will be demonstrated if the lower limit of the two-sided asymptotic standardized 95% CI for the difference in seroconversion rate between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and licensed lyophilised HRV vaccine is greater than or equal to -10%.

- To demonstrate the non-inferiority of the PCV-free liquid HRV vaccine to that of the currently licensed lyophilised HRV vaccine in terms of serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the ratio of anti-RV IgA antibody GMCs 1-2 months after Dose 2 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and the lyophilised HRV vaccine is greater than or equal to 0.67.

3.2. Secondary

Reactogenicity and safety

- To evaluate the reactogenicity of the liquid HRV vaccine and currently licensed lyophilised HRV vaccine in terms of solicited AEs during the 8 days (Day 0-Day 7) follow-up period after each vaccination.
- To assess the safety of the study vaccines in terms of unsolicited AEs during the 31 days (Day 0-Day 30) follow-up period after each vaccination and Serious Adverse Events (SAEs) during the entire study period.

Immunogenicity

- To assess the immunogenicity of the PCV-free liquid HRV vaccine and the currently licensed lyophilised HRV vaccine, in terms of percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2.

4. ENDPOINTS

4.1. Primary

- Evaluation of immunogenicity in terms of anti-RV antibody concentrations
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in each of the HRV liquid formulation groups (Liq_A, Liq_B and Liq_C).
  - Anti-RV IgA antibody seroconversion rate* 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
  - Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

*Seroconversion rate is defined as the percentage of subjects who were initially seronegative (i.e., with anti-RV IgA antibody concentration < 20 U/mL prior the first dose of HRV vaccine) and developed anti-RV IgA antibody concentration ≥ 20 U/mL at Visit 3.

4.2. Secondary

- Solicited adverse events
  - Occurrence of each general solicited symptom within the 8 days (Day 0-Day 7) follow-up period after each dose of the lyophilised and PCV-free HRV liquid vaccine
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs within 31 days (Day 0-Day 30) after any dose of HRV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events
  - Occurrence of serious adverse events from Dose 1 up to study end.
- Evaluation of immunogenicity in terms of anti-RV antibody concentrations.
  - Serum anti-RV IgA antibody concentrations ≥ 90 U/mL 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

5. ANALYSIS SETS

5.1. Definitions

5.1.1. Exposed Set

The ES will include all subjects with at least one study vaccine administration documented:

- a safety analysis based on the ES will include all vaccinated subjects,
- an immunogenicity analysis based on the ES will include all vaccinated subjects for whom immunogenicity data are available.

The ES analysis will be performed per treatment actually administered at dose 1.

5.1.2. Per-Protocol analysis Set of immunogenicity (PPS)

The PPS for immunogenicity will include all subjects from the ES:

- who have received all doses of study vaccine,
- for whom the HRV vaccine liquid or lyophilised formulation was administered according to protocol and subjects did not regurgitate after vaccination,
- who have not received a vaccine prohibited by the protocol up to Visit 3,
- for whom the randomisation code has not been broken
- who were seronegative for serum anti-RV IgA antibodies on the day of Dose 1
- who have not received medication prohibited by the protocol up to Visit 3 as listed in Section 6.7.2 of the study protocol,
- whose underlying medical condition was not prohibited by the protocol up to Visit 3 as listed in Section 6.8 of the study protocol,
- who comply with the vaccination schedule (Table 5 of the study protocol),
- who comply with blood sampling schedule (Table 5 of the study protocol),
- for whom immunogenicity data are available at the post-vaccination sampling time point,
- who have no RV other than vaccine strain in Gastroenteritis (GE) stool samples collected up to Visit 3,
- who have no concomitant infection unrelated to the vaccine up to Visit 3, which may influence the immune response.

5.2. Criteria for eliminating data from analyses sets

5.2.1. Elimination from Exposed set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Per-Protocol analysis Set (PPS)

A subject will be excluded from the PPS analysis under the following conditions

Code	Decode => Condition under which the code is used
900	Questionable subject => subjects with invalid informed consent or fraudulent data
1030	Study vaccine dose not administrated but subject number allocated => subjects enrolled but not vaccinated
1040	Administration of vaccine(s) forbidden in the protocol => Administration of a vaccine not foreseen by the study protocol and administered during the period starting from 30 days before the first vaccination and ending at Visit 3, with the exception of the inactivated influenza vaccine, which is allowed at any time during the study, and other licensed routine childhood vaccinations.
1060	Randomisation code broken at the investigator site => Subjects unblinded in SBIR or unblinding reported as protocol deviation
1070	Study vaccine dose not administered according to protocol => • Subjects vaccinated with the correct vaccine but who regurgitated for one of the 2 doses; • subjects for whom the second administered dose is not aligned with the first dose (e.g. lyo as second dose after a first dose with liquid from lot A; or liquid from lot B as second dose after a first dose with liquid from lot A) • Subject who did not receive the second dose and return to visit 3 blood sample • Subject who was given multiple doses at one visit • Route of vaccination which is not oral
1080	Vaccine temperature deviation => Subjects who have received a vaccine which had a temperature deviation qualified as inappropriate for use by Quality Assurance.
1090	Expired vaccine administered => Subjects who received an expired vaccine

Code	Decode => Condition under which the code is used
2010	Protocol violation (inclusion/exclusion criteria) => Ineligible subjects who was vaccinated (i.e. Age at dose 1 is not between 42-90 days, gestational age is < 37 weeks 0 day or > 41 weeks 6 days or other eligibility criteria – see section 4.2 and 4.3 of the protocol)
2020	Initially seropositive or initially unknown antibody status = > Anti-HRV concentration ≥ 20 U/mL or unknown at pre-dose 1 blood sample
2040	Administration of any medication forbidden by the protocol => administration of • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used between Visit 1 and Visit 3 during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period between Visit 1 to Visit 3. For corticosteroids, this will mean prednisone (0.5 mg/kg/day, or equivalent). Inhaled and topical steroids are allowed. • Immunoglobulins and/or any blood products administered during the study period between Visit 1 to Visit 3. • Long-acting immune-modifying drugs administered at any time during the study period (e.g., infliximab).
2060	Concomitant infection related to the vaccine which may influence immune response => Subjects with non-vaccine type RV detected in GE stool samples that may impact immunogenicity at Visit 3.
2070	Concomitant infection not related to the vaccine which may influence immune response = > Condition that has the capability of altering their immune response at visit 3 such autoimmune disease.
2080	Non-compliance with vaccination schedule (including wrong and unknown dates) => Subjects who did not comply with the interval for dose 2 (Dose 2 should be between 28-83 days after Dose 1).
2090	Non-compliance with blood sampling schedule (including wrong and unknown dates => Subjects who did not comply with the blood sample interval (blood sample post dose 2 should be between 28-83 days after Dose 2); subjects with a blood sample at visit 3 and without a second HRV vaccine administered
2100	Essential serological data missing => Anti-HRV results not available post-vaccination
2120	Obvious incoherence or abnormality or error in data => subjects without blood sample at visit 3 for whom a sample post-vaccination is found.

5.2.3. Right censored Data

Not applicable

5.2.4. Visit-specific censored Data

Not applicable

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

The following important protocol deviations will be reported by groups:

- Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.
- Manual randomization: In case the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule. In case the randomization system is available, a vaccine different from the randomized treatment may have been administered at dose 1.
- Short follow-up: subjects with a safety follow-up period after the last dose of HRV vaccine that is less than 180 days.
- Vaccinated subjects without documentation of solicited symptoms i.e. for a vaccine dose administered, at least one solicited symptom is not documented as being present or absent.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Annex 1 and will not be repeated below. All Confidence Interval (CI) will be two-sided 95% CI.

6.1. Demography

6.1.1. Analysis of demographics/baseline characteristics planned in the protocol

The following calculations will be performed for each group and for the pooled liquid vaccine group:

- The distribution of subjects enrolled among the study centres and countries will be tabulated as a whole and for each group.
- The numbers of subjects who withdraw 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.
- The median, mean, range and standard deviation of age (in weeks) at each HRV vaccine dose and of the gestational age will be computed by group. The median, mean and standard deviation of height (in centimetres) and weight (in kilograms) at

Visit 1 will be computed by group. The racial and sex composition will be presented. These calculations will also be performed by country.

- Summary of co-administered vaccinations (i.e., vaccinations given on the day of each HRV vaccine dose) and intercurrent vaccinations (i.e., vaccinations from birth up to Visit 3, excluding vaccination given on the day of HRV vaccine doses) will be summarized by group for the ES.

6.1.2. Additional considerations

All demography summaries will be generated for the ES. The summary of age, height, weight, race and sex will also be provided for the PPS. Number and reason for elimination from PPS will be tabulated by group. Summary of important protocol deviations not leading to elimination will be provided by groups for the PPS.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

Not applicable

6.2.2. Additional considerations

The number of doses administered will be tabulated for each group.

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the PPS for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.

6.3.1.1. Within groups assessment

The following calculations will be performed for each group and for the pooled liquid vaccine group.

- For each group, at each time point that anti-rotavirus IgA is measured,
  - Seropositivity/seroconversion rates and their exact 95% CI will be computed,
  - Percentage of subjects with anti-RV IgA antibody concentrations ≥ 90 U/mL and their exact 95% CI will be computed.
  - GMCs and their 95% CIs will be computed.
- The above mentioned descriptive analyses will also be performed by country.

- The distribution of anti-RV IgA antibody concentrations at Visit 3 will be displayed using Reverse Cumulative Curves (RCCs).

6.3.1.2. Between groups assessment

- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between any pair of the three lots of the HRV liquid vaccine will be computed (first co-primary objective).
- The asymptotic standardized 95% CI for the difference in seroconversion rate at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine will be computed (second co-primary objective).
- The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine will be computed (third co-primary objective).

6.3.1.3. Statistical Methods

- The exact CIs for a proportion within a group will be calculated using SAS [see section 11.1].
- The standardized asymptotic CI for the group difference in proportion will be calculated using SAS [see section 11.1].
- The CI for GMCs will be obtained within each group separately. The CI for the mean of log-transformed concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The CI for the GMCs will then be obtained by exponential-transformation of the CI for the mean of log-transformed concentration.
- The GMC group ratio will be obtained using an ANOVA model on the logarithm-transformed concentrations. The ANOVA model will include the vaccine group and the country as fixed effects. The GMC ratio and their 95% CI will be derived by exponential-transformation of the corresponding group contrast in the model.

6.3.2. Additional considerations

The ANOVA model for the lot-to-lot GMC ratio will include the data from the 3 HRV liquid groups only.

The country effect for the ANOVA model will be accounted by country indicator variables that will be treated as continuous variable in order to obtain adjusted GMCs that reflect the distribution of subjects between countries.

Summaries planned per countries will be limited to the PPS. These summaries will also be generated by frequent race and by gender. Note that a race category is considered if it includes more than 40 subjects. Infrequent race categories will be combined together and summarized if it includes more than 40 subjects.

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

The ES will be used for the analysis of safety.

The following calculations will be performed for each group and for the pooled liquid vaccine group:

The percentage of doses and of subjects reporting at least one symptom (solicited or unsolicited) during the 8 days (Day 0-Day 7) solicited follow-up period post vaccination will be computed, along with exact 95% CI. The same calculations will be done for symptoms (solicited or unsolicited) rated as grade 3 in intensity and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.

The percentage of doses and of subjects reporting each individual solicited general symptom will be computed, over the 8 days (Day 0-Day 7) solicited follow-up period post vaccination, along with exact 95% CI. The same calculations will be done for each individual general solicited symptom rated as grade 3 in intensity, for each individual solicited general symptom assessed as causally related to vaccination and those that resulted in a medically attended visit.

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 days (Day 0-Day 30) 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, for unsolicited AEs with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of subjects reporting GE episodes from Dose 1 of HRV vaccine up to Visit 3 will be tabulated by group.

The percentage of subjects with presence of RV in GE stool samples collected from Dose 1 of HRV vaccine up to Visit 3 will be tabulated by group.

The percentage of GE episodes with no available stool results from Dose 1 of HRV vaccine up to Visit 3 will be tabulated.

The percentage of subjects who started taking at least one concomitant medication from HRV vaccination to Day 7 after vaccinations will be tabulated with exact 95% CI. The percentages of subjects who started taking at least one concomitant medication during the study period will be tabulated with exact 95% CI.

SAEs reported during the study period will be described in detail.

6.4.2. Additional considerations

As indicated in section 10.5 of the protocol and in line with the project history, analysis of safety will be primarily performed per dose administered and subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). A sensitivity analysis will be performed on documented doses i.e. accounting only for doses where solicited symptoms are indicated as being absent/present in case more than 5% of the doses are not documented.

Summary of temperature will be provided by 0.5° increment (i.e. ≥ 38.0°C, >38.5; > 39, > 39.5, > 40).

Gastroenteritis is assumed to take place when either:

- a stool collection is reported
- three or more than 3 loose stools are reported as solicited diarrhoea symptom.
- an unsolicited symptom, which has an onset date more than 7 days after vaccination (i.e. with onset day > 8), is associated with the high lever MedDRA terms hereunder but excluding Diarrhoea as primary preferred term (10012735): 'Gastric and gastroenteric infections' (10017887),'Gastrointestinal infections, site unspecified' (10017968), 'Intestinal infections (10022678)', 'Faecal, abnormalities NEC' (10016097), 'Diarrhoea (excl infective)' (10012736).

Summary of solicited symptoms will also be provided by country, gender and frequent race(s) while summary of unsolicited symptoms within 31 days post-vaccination will be provided by country – see section 6.3.2 for the definition of frequent race.

Summary of solicited symptoms will also be provided for each individual general solicited symptom causally related to vaccination and rated as grade 3 in intensity. Likewise the percentage of subjects and of doses with grade 3 causally related unsolicited AEs occurring within 31 days (Day 0-Day 30) follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. These summaries will not be provided by country, gender or frequent race(s).

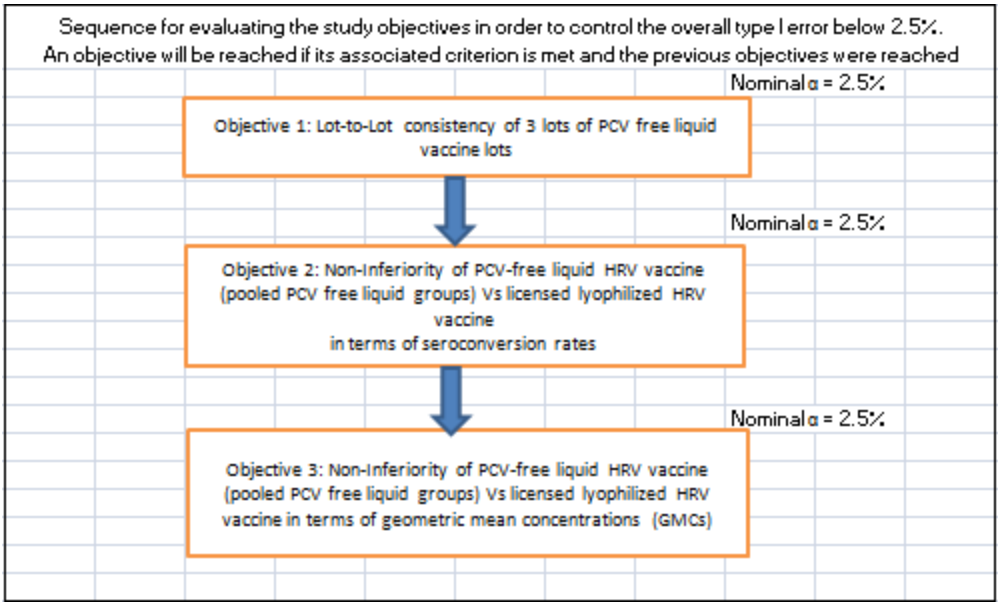
Note that the study will be converted in cDISC. Accordingly Day 0-Day 7 and Day 0-Day 30 will be replaced by Day 1-Day 8 and Day 1-Day 31 for the statistical analysis.

7. ANALYSIS INTERPRETATION

Except for analyses addressing criteria specified in the co-primary objectives referred as confirmatory analyses, all the analyses will be descriptive/exploratory in nature. The use of these descriptive/exploratory analyses should be limited to support the confirmatory analyses or to generate hypothesis.

To control the overall type I error below 2.5%, the confirmatory objectives will be evaluated using a hierarchical procedure as shown in Figure 1. A confirmatory objective will be reached if the associated criteria are met and the previous objectives have been met.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%



8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Safety data that is as clean as possible will be analysed for IDMC review. Details of the review are described in an IDMC charter.

8.1.1. Final analysis up to Visit 3:

An analysis will be conducted once all the study data up to Visit 3 are available and cleaned and Rota-IgA ELISA testing at 1-2 month post-dose 2 has been fully completed. The Clinical Study Report (CSR) with data up to Visit 3 will be used for the registration of PCV-free liquid vaccine in European Union (EU) and 'rest of world' countries.

The study report will include the following:

- All analysis of the serum anti-RV IgA antibody concentrations, 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.
- All analyses of safety up to visit 3 and analysis of SAEs and AEs leading to drop out based on the database lock for the analysis.

8.2. Final analysis

If the previous analysis does not cover all study data, the study report will be amended when all data will be available. The study report amendment will include the additional safety information

The following table provides the plan for analyses excluding analyses dedicated to IDMC

Description	Analysis ID	Disclosure Purpose (IN=internal, CTRS=public posting, SR=study report and public posting)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis up to Visit 3	E1_05	SR	Yes	Yes	TFL TOC first version – All TFLs as per database lock date
Final	E1_01	SR	No	Yes	TFL TOC first version - All TFLs

8.3. Statistical considerations for interim analyses

All confirmatory analyses will be conducted for the Final analysis up to Visit 3 and therefore no statistical adjustment for interim analyses is required.

9. CHANGES FROM PLANNED ANALYSES

Not applicable

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The mock tables referred under column named 'layout' can be found in Annex 3 of this SAP.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
1	Liq_A	PCV-free HRV liquid vaccine - lot A
2	Liq_B	PCV-free HRV liquid vaccine - lot B
3	Liq_C	PCV-free HRV liquid vaccine - lot C
4	Liq pooled	PCV-free HRV liquid vaccine - Pooled Lot
5	Lyo	HRV Lyophilised vaccine

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413.

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med.* 1998; 17, 873-890. The standardised asymptotic method used is the method six.

11.1.1. Date derivation

- SAS date derived from a character date: in case day is missing, PPD is used. In case day & month are missing, PPD is used.
- Onset day for an event (ae, medication, vaccination, …): the onset day is the number of days between the last study vaccination & the onset/start date of the event. This is 1 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.

11.1.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 1 refers to all vaccines administered at the first vaccination visit while dose 2 corresponds to all vaccinations administered at the second vaccination visit even if this is the first time a product is administered to the subject.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered and an event occurs after the subsequent study dose (e.g. 2nd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g. dose 2).
- The number of doses for a product is the number of time the product was administered to a subject.
- The incidence per dose is the number of vaccination visits at which an event was reported among all vaccination visits.

11.1.3. Demography

Age: Age at the reference activity, computed as the number of complete weeks between the date of birth and the reference activity.

Conversion of weight to kg: the following conversion rule is used:

Weight in Kilogram= weight in Pounds / 2.2

Weight in Kilogram =weight in ounces / 35.2

The result is rounded to 2 decimals.

Conversion of height to cm: the following conversion rule is used:

Height in Centimetres = Height in Feet * 30.48

Height in Centimetres = Height in Inch * 2.54

The result is rounded to the unit (i.e. no decimal).

Conversion of temperature to °C: the following conversion rule is used:

Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

The result is rounded to 1 decimal.

11.1.4. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.
- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3 of the protocol.
- A seronegative subject is a subject whose antibody concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody concentration is greater than or equal to the cut-off value of the assay.
- The assay cut-off is the value under which there is no quantifiable result available. For an assay with a specific 'cut_off' , numerical immuno result is derived from a character field (rawres):
  - If rawres is 'NEG' or '-' or '(-)', numeric result= cut_off/2,
  - if rawres is 'POS' or '+' or '(+)', numeric result = cut_off,
  - if rawres is '< value' and value<=cut_off, numeric result =cut_off/2,
  - if rawres is '< value' and value>cut_off, numeric result =value,
  - if rawres is '> value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '> value' and value>=cut_off, numeric result =value,
  - if rawres is '<= value' or '>= value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '<= value' or '>= value' and value>=cut_off, numeric result =value,
  - if rawres is a value < cut_off, numeric result = cut_off/2,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - else numeric result is left blank.

11.1.5. Safety

- For analysis of solicited, unsolicited adverse events (such as serious adverse events or adverse events by primary MedDRA term) and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- In case there will be more than 5% of subjects without documented dose for solicited symptoms (i.e., symptom screen not completed), sensitivity analysis will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed).

- The following rules will be used for the analysis of solicited symptoms:
  - Subject who didn't document the presence or absence of a solicited symptom after one dose will be considered not having that symptom after that dose in the analysis done on "administrated dose"
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
  - Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
  - Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be considered as having that symptom after that dose).
- For the analysis, temperatures will be coded as follows for oral, axillary or tympanic route:

Grade	Temperature
0	< 38.0°C
1	≥ 38.0°C - ≤ 38.5°C
2	> 38.5°C - ≤ 39.5°C
3	> 39.5°C

- Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	**N used for deriving % per subject for Vaccination phase**	**N used for deriving % per dose for Vaccination phase**
Concomitant vaccination	All subjects with study vaccine administered	All study visits with study vaccine administered
Solicited general symptom	Primary analysis: all subjects with study vaccine administered Sensitivity analysis as applicable (see section 6.4.2): all subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	Primary analysis: all study visits with study vaccine administered Sensitivity analysis: all study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered
Concomitant medication	All subjects with study vaccine administered	All study visits with study vaccine administered

For summaries by MedDRA primary preferred term combining solicited and unsolicited adverse events, solicited adverse events will be coded as per the following MedDRA codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Fever	10016558	Fever
Irritability/Fussiness	10022998	Irritability
Diarrhoea	10012727	Diarrhoea
Vomiting	10047700	Vomiting
Loss of appetite	10003028	Appetite lost
Cough/runny nose	10011224	Cough

11.1.6. Management of missing data

Demography:

- For a given subject and a given demographic variable, missing measurements will not be replaced.

Immunogenicity:

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

Reactogenicity and safety:

- Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

11.1.7. Data presentation description

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
Demographic characteristics	Mean, median, SD	1
Immunogenicity	% of difference, including LL & UL of CI	2
Immunogenicity	GMC group ratio, including LL & UL of CI	2
Immunogenicity	Anti-RV IgA GMC	1

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to Section 5.2.

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used.

The data display, title and footnote are for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC.

These templates were copied from ROTA-061 and additional tables required for public disclosure were added. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs. These editorial/minor changes will not lead to a SAP amendment.

Note that all tables will include the pooled lot group for HRV liquid as shown in Template 2.

Template 1 Minimum and maximum activity dates (Exposed Set)

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

*Database Lock Date = 31MAR2009

Template 2 Number of subjects enrolled by center - Exposed Set

Country	Center	LIQ_A	LIQ_B	LIQ_C	LIQ_pool	LYO	Total	
		n	n	n	n	n	n	%
XXXX	PPD	38	38	38		37	151	12.6
	PPD	20	20	20		20	80	6.7
	PPD	30	30	29		29	118	9.8
	PPD	19	19	20		20	78	6.5
	All							
YYYYY	PPD	15	15	15		15	60	5.0
	PPD	22	22	23		22	89	7.4
	PPD	35	36	36		35	142	11.8
	PPD	28	28	28		28	112	9.3
	PPD	20	21	20		21	82	6.8
	PPD	22	23	22		23	90	7.5
	PPD	22	23	22		23	90	7.5
	PPD	27	27	27		27	108	9.0
	All							
All	All	298	302	300		300	1200	100

<group description >
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

Template 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal entire study period- Exposed Set

	LIQ_A	LIQ_B	LIQ_C	LYO	Total
Number of subjects vaccinated	298	302	300	300	1200
Number of subjects completed	297	301	298	297	1193
Number of subjects withdrawn	1	1	2	3	7
Reasons for withdrawal :					
Serious Adverse Event	0	0	0	1	1
Non-serious adverse event	0	0	0	0	0
Protocol violation	0	0	0	0	0
Consent withdrawal (not due to an adverse event)	1	0	1	2	4
Migrated/moved from study area	0	1	1	0	2
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	0	0	0	0
Others	0	0	0	0	0

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed study visit 3
Withdrawn = number of subjects who did not come for study visit 3

Template 4 Number of subjects at each visit and list of withdrawn subjects (Exposed Set)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
Liq_A	VISIT 1	508		
			no. PP	CONSENT WITHDRAWAL
			no. PP	CONSENT WITHDRAWAL
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	CONSENT WITHDRAWAL
	VISIT 2	504		
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	SERIOUS ADVERSE EXPERIENCE
	VISIT 3	501		
			no. P	MIGRATION FROM STUDY AREA
			no. PP	CONSENT WITHDRAWAL
			no. PP	MIGRATION FROM STUDY AREA
			no. PP	CONSENT WITHDRAWAL
			no. PP	MIGRATION FROM STUDY AREA
			no. PP	MIGRATION FROM STUDY AREA
			no. PPD	CONSENT WITHDRAWAL
			no. PPD	MIGRATION FROM STUDY AREA
			no. PPD	MIGRATION FROM STUDY AREA
	VISIT 4	492		
Lyo	VISIT 1	257		
			no. PP	PROTOCOL VIOLATION
			no. PPD	CONSENT WITHDRAWAL
	VISIT 2	255		
			no. PPD	CONSENT WITHDRAWAL
	VISIT 3	254		
			no. PPD	MIGRATION FROM STUDY AREA
			no. PP	LOST TO FOLLOW-UP
			no. PPD	LOST TO FOLLOW-UP
			no. PP	CONSENT WITHDRAWAL
			no. PP	MIGRATION FROM STUDY AREA
			no. PPD	LOST TO FOLLOW-UP
			no. PPD	ADVERSE EXPERIENCE
	VISIT 4	247		

Template 5 Number of subjects enrolled into the study as well as the number of subjects excluded from PPS analyses with reasons for exclusion

	Total				LIQ_A			LIQ_B			LIQ_C			LYO		
Title	**N**	**n**	**s**	**%**	**N**	**n**	**s**	**N**	**n**	**s**	**N**	**n**	**s**	**N**	**n**	**s**
Total enrolled cohort	**1200**				**298**			**302**			**300**			**300**		
Exposed Set	**1200**			**100**	**298**			**302**			**300**			**300**		
Administration of vaccine(s) forbidden in the protocol (code 1040)		2	2			1	1		1	1		0	0		0	0
Study vaccine dose not administered according to protocol (code 1070)		73	73			21	21		13	13		23	23		16	16
Initially seropositive or unknown anti-rotavirus IgA antibody on day of dose 1 (code 1500)		10	11			3	4		3	3		3	3		1	1
Protocol violation (inclusion/exclusion criteria) (code 2010)		1	1			0	0		0	0		1	1		0	0
Administration of any medication forbidden by the protocol (code 2040)		1	1			0	0		0	0		0	0		1	1
Underlying medical condition forbidden by the protocol (code 2050)		1	1			1	1		0	0		0	0		0	0
Concomitant infection not related to the vaccine which may influence immune response (code 2070)		0	1			0	0		0	0		0	0		0	1
Non-compliance with vaccination schedule (including wrong and unknown dates) (code 2080)		14	16			5	5		0	0		6	7		3	4
Non-compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)		12	16			2	3		3	3		3	5		4	5
Essential serological data missing (code 2100)		87	95			23	25		21	22		20	22		23	26
Subjects with incomplete study vaccination schedule but with post serological result (code 2500)		1	1			0	0		1	1		0	0		0	0
Per protocol set	**998**			**83.2**	**242**			**260**			**244**			**252**		

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LYO = HRV vaccine lyophilised formulation
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 per protocol set (PPS) relative to the exposed set (ES)

Template 6 Summary of demographic characteristics (Per Protocol Analysis Set of Immunogenicity)

		LIQ_A N = 242		LIQ_B N = 260		LIQ_C N = 244		LYO N = 252		Total N = 998	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 of HRV vaccine (weeks)	Mean	11.6	-	11.5	-	11.5	-	11.6	-	11.6	-
	SD	1.32	-	1.16	-	1.19	-	1.20	-	1.22	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	10	-	10	-	10	-	10	-	10	-
	Maximum	17	-	15	-	15	-	16	-	17	-
Age at Dose 2 of HRV vaccine (weeks)	Mean	16.6	-	16.5	-	16.5	-	16.7	-	16.6	-
	SD	1.48	-	1.40	-	1.37	-	1.34	-	1.40	-
	Median	17.0	-	16.0	-	16.0	-	17.0	-	17.0	-
	Minimum	14	-	14	-	14	-	14	-	14	-
	Maximum	22	-	20	-	20	-	21	-	22	-
Gender	Female	122	50.4	121	46.5	120	49.2	120	47.6	483	48.4
	Male	120	49.6	139	53.5	124	50.8	132	52.4	515	51.6
Ethnicity	American Hispanic or Latino	0	0.0	2	0.8	1	0.4	0	0.0	3	0.3
	Not American Hispanic or Latino	242	100.0	258	99.2	243	99.6	252	100.0	995	99.7
Race	African heritage / African American	1	0.4	0	0.0	1	0.4	0	0.0	2	0.2
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - central/south Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - south east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / north African heritage	0	0.0	0	0.0	2	0.8	0	0.0	2	0.2
	White - Caucasian / European heritage	239	98.8	258	99.2	240	98.4	247	98.0	984	98.6
	Other	2	0.8	2	0.8	1	0.4	5	2.0	10	1.0
Height at Visit 1 (cm)	Mean	60.4	-	60.5	-	60.7	-	60.6	-	60.5	-
	SD	2.35	-	2.37	-	2.32	-	2.22	-	2.32	-
	Median	61.0	-	60.0	-	61.0	-	61.0	-	61.0	-
	Unknown	0	-	1	-	2	-	0	-	3	-
Weight at Visit 1 (kg)	Mean	6.0	-	6.1	-	6.2	-	6.1	-	6.1	-
	SD	0.77	-	0.76	-	0.77	-	0.75	-	0.76	-
	Median	6.0	-	6.0	-	6.2	-	6.1	-	6.1	-
BMI at Visit 1 (kg/m^2)	Mean	16.5	-	16.6	-	16.7	-	16.7	-	16.6	-
	SD	1.49	-	1.46	-	1.46	-	1.46	-	1.47	-
	Median	16.3	-	16.5	-	16.5	-	16.7	-	16.5	-
	Unknown	0	-	1	-	2	-	0	-	3	-

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C

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

Template 7 Deviations from specifications for age and intervals between study visits - Exposed Set

		Age	PRE-Dose:1	Dose:1-Dose:2		Dose:2-PII(M2)	
Group		**Protocol**	**Protocol**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
		from 10 to 17 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**
LIQ_A	**N**	298	298	297	297	287	287
	n	0	2	8	7	1	1
	%	0.0	0.7	2.7	2.4	0.3	0.3
	range	10 to 17	0 to 4	29 to 76	29 to 76	30 to 55	30 to 55
LIQ_B	**N**	302	302	301	301	294	294
	n	0	1	0	0	4	2
	%	0.0	0.3	0.0	0.0	1.4	0.7
	range	10 to 15	0 to 3	30 to 48	30 to 48	24 to 56	24 to 56
LIQ_C	**N**	300	300	300	300	291	291
	n	1	1	8	7	4	4
	%	0.3	0.3	2.7	2.3	1.4	1.4
	range	9 to 17	0 to 9	27 to 76	27 to 76	30 to 56	30 to 56
LYO	**N**	300	300	299	299	289	289
	n	0	2	4	4	5	3
	%	0.0	0.7	1.3	1.3	1.7	1.0
	range	10 to 16	0 to 3	30 to 61	30 to 61	28 to 61	28 to 61

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
PRE = pre-vaccination
PII (M2) = blood sample taken one month after Dose 2 of the HRV vaccine (Visit 3)
Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals

Template 8 Summary of co-administered vaccination by dose - Exposed Set

Dose1	LIQ_A N = 298		LIQ_B N = 302		LIQ_C N = 300		LYO N = 300		Total N = 1200	
Characteristics	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Any	298	100	302	100	299	99.7	300	100	1199	99.9
Infanrix hexa	298	100	302	100	299	99.7	300	100	1199	99.9
Dose 2	**LIQ_A N = 297**		**LIQ_B N = 301**		**LIQ_C N = 300**		**LYO N = 299**		**Total N = 1197**	
Characteristics	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Any	297	100	301	100	298	99.3	299	100	1195	99.8
Infanrix hexa	297	100	301	100	298	99.3	299	100	1195	99.8

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
N = total number of subjects having received the considered dose of HRV
n/% = number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV vaccine

Template 9 Summary of vaccinations other than HRV vaccine administered from birth until Visit 3, excluding vaccination given on the day of HRV doses - Exposed Set

Before Dose 1	LIQ_A N = 298			LIQ_B N = 302			LIQ_C N = 300			LYO N = 300			Total N = 1200		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	18	18	6.0	11	11	3.6	13	13	4.3	25	25	8.3	67	67	5.6
BCG	18	18	6.0	11	11	3.6	12	12	4.0	25	25	8.3	66	66	5.5
Infanrix hexa™	0	0	0.0	0	0	0.0	1	1	0.3	0	0	0.0	1	1	0.1
Between Dose 1 and Dose 2§	**LIQ_A N = 298**			**LIQ_B N = 302**			**LIQ_C N = 300**			**LYO N = 300**			**Total N = 1200**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**n**	**%**
Any	0	0	0.0	2	1	0.3	0	0	0.0	0	0	0.0	2	1	0.1
Infanrix hexa™	0	0	0.0	2	1	0.3	0	0	0.0	0	0	0.0	2	1	0.1
Between Dose 2 and Visit 3*	**LIQ_A N = 297**			**LIQ_B N = 301**			**LIQ_C N = 300**			**LYO N = 299**			**Total N = 1197**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**n**	**%**
Any	291	291	98.0	295	295	98.0	287	286	95.3	290	290	97.0	1163	1162	97.1
DTPa+IPV+Hib	0	0	0.0	1	1	0.3	0	0	0.0	0	0	0.0	1	1	0.1
Infanrix hexa™	291	291	98.0	294	294	97.7	287	286	95.3	290	290	97.0	1162	1161	97.0

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LYO = HRV vaccine lyophilised formulation
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
§= up to last contact of conclusion at Visit 3 if dose 2 of HRV was not administered
*= up to last contact of conclusion at Visit 3 if visit 3 was not done

Template 10 Anti-rotavirus IgA antibody GMC and seroconversion rates – Per Protocol Analysis Set of Immunogenicity

			≥ 20 U/ml				GMC (U/ml)		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
LIQ_A	PRE	242	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	242	220	90.9	86.6	94.2	384.4	309.1	478.2
LIQ_B	PRE	260	0	0.0	0.0	1.4	<20	-	-
	PII(M2)	260	235	90.4	86.1	93.7	418.8	337.8	519.1
LIQ_C	PRE	244	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	244	206	84.4	79.3	88.7	324.4	253.4	415.3
LIQPOOL	PRE	746	0	0.0	0.0	0.5	<20	-	-
	PII(M2)	746	661	88.6	86.1	90.8	374.7	328.8	426.9
LYO	PRE	252	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	252	228	90.5	86.2	93.8	331.8	265.0	415.4

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects with available results
n (%) = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L =Lower limit; U.L = upper limit
Pre = pre-vaccination
PII (M2) = blood sample taken one month after Dose 2 of HRV vaccine (Visit 3)

Template 11 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies – Per Protocol Analysis Set of Immunogenicity

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
LIQ_A	PII(M2)	220	553.8	463.4	661.7
LIQ_B	PII(M2)	235	623.0	525.0	739.4
LIQ_C	PII(M2)	206	616.4	510.4	744.4
LIQPOOL	PII(M2)	661	597.1	538.7	661.8
LYO	PII(M2)	228	479.7	395.4	582.0

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; LL = Lower Limit; UL = Upper Limit
PII(M2) = blood sample taken one month after Dose 2 of HRV vaccine (Visit 3)

Template 12 Ratio of anti-rotavirus IgA antibody GMCs 1-2 months after Dose 2 of the HRV vaccine between each pair of the three lots of the HRV PCV-free liquid vaccine – Per Protocol Analysis Set of Immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
LIQ_A	242	384.4	**LIQ_B**	260	418.8	**LIQ_A /LIQ_B**	0.92	0.67*	1.26*
LIQ_A	242	384.4	**LIQ_C**	244	324.4	**LIQ_A /LIQ_C**	1.19	0.86*	1.64*
LIQ_B	260	418.8	**LIQ_C**	244	324.4	**LIQ_B /LIQ_C**	1.29	0.94*	1.77*

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects with available results
95% CI = 95% Confidence Interval (one-way ANOVA model with pooled variance from the four groups)
L.L. = Lower Limit, U.L. = Upper Limit
*The two-sided 95% CIs are within [0.5; 2] (the pre-defined clinical limit interval for consistency)

Template 13 Difference between groups in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody 1-2 months after Dose 2 of the HRV vaccine – Per Protocol Analysis Set of Immunogenicity

						Difference in seroconversion rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
LIQPOOL	746	88.6	**LYO**	252	90.5	**LYO - LIQPOOL**	1.87	-2.85	5.83*

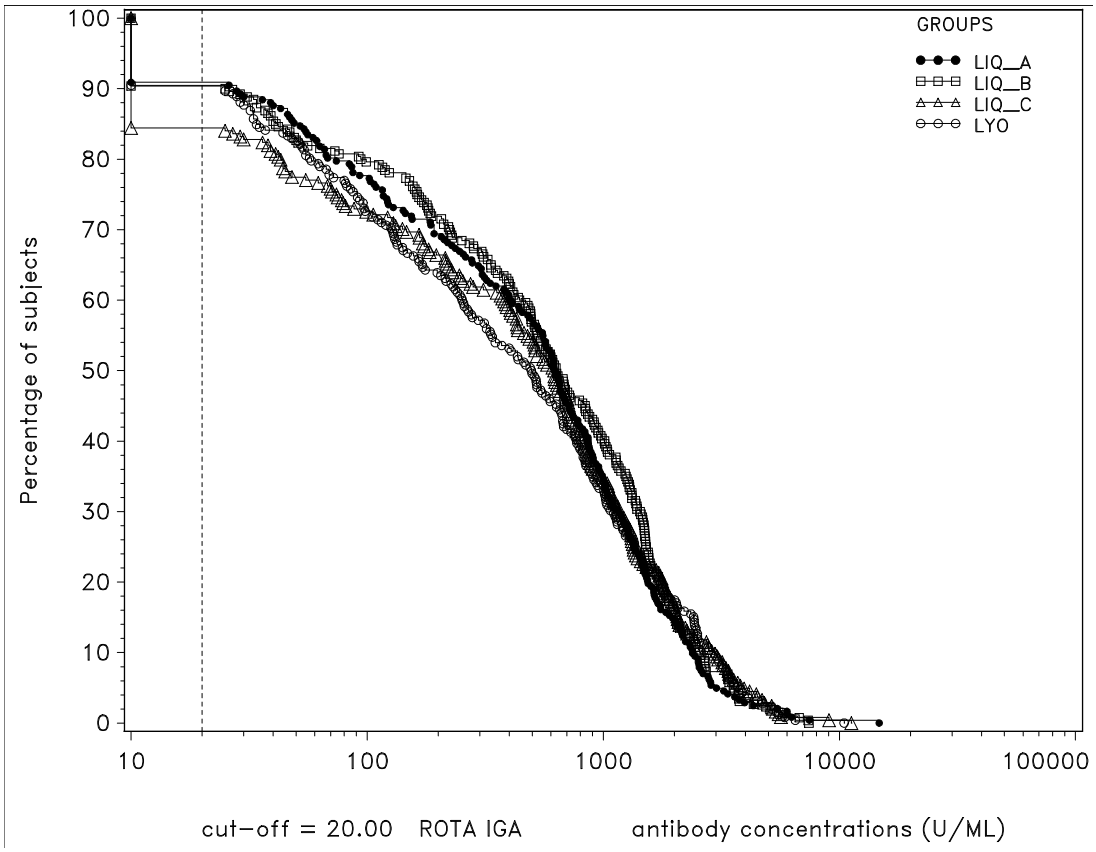
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects with available results
% = percentage of subjects who seroconverted at visit 3
95% CI = asymptotic standardised 95% Confidence Interval; LL = Lower Limit; UL = Upper Limit
*Lower limit of the 95% CI ≥-10% (the pre-defined clinical limit for non-inferiority)

Template 14 Ratio of anti-rotavirus IgA antibody GMCs 1-2 months after Dose 2 of the HRV vaccine between the HRV lyophilised vaccine group and the pooled HRV PCV-free liquid vaccine – Per Protocol Analysis Set of Immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
LIQPOOL	746	373.8†	LYO	252	331.8	LYO /LIQPOOL	0.89	0.68	1.15*

LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects with available results
†geometric mean of the 3 GMC from the HRV liquid formulation groups
95% CI = 95% Confidence Interval (one-way ANOVA model using the group contrast between the HRV lyophilised formulation group and average of the HRV liquid formulation groups)
L.L. = Lower Limit, U.L. = Upper Limit
*Lower limit of the 95% CI ≥ 0.67 (the pre-defined clinical limit for non-inferiority)

Template 15 Reverse cumulative distribution curve for anti-rotavirus IgA antibody concentrations at Visit 3 - Per Protocol Analysis Set of Immunogenicity



Template 16 Number and percentage of subjects who received study vaccine doses - Exposed Set

	LIQ_A N = 298		LIQ_B N = 302		LIQ_C N = 300		LYO N = 300		Total N = 1200	
Total number of doses received	n	%	n	%	n	%	n	%	n	%
1	1	0.3	1	0.3	0	0.0	1	0.3	3	0.3
2	297	99.7	301	99.7	300	100	299	99.7	1197	99.8
Any	298	100	302	100	300	100	300	100	1200	100

LIQ_A = HRV vaccine Liquid formulation lot A LIQ_B = HRV vaccine Liquid formulation lot B
LIQ_C = HRV vaccine Liquid formulation lot C LYO = HRV vaccine lyophilised formulation
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

Template 17 Compliance in returning symptom sheets - Exposed Set

Dose	GROUP	Number of doses	Doses NOT according to protocol	Number of general SS	Compliance % general SS
1	LIQ_A	298	10	298	100
	LIQ_B	302	7	302	100
	LIQ_C	300	6	300	100
	LIQPOOL	900	23	900	100
	LYO	300	6	299	99.7
2	LIQ_A	297	12	296	99.7
	LIQ_B	301	6	301	100
	LIQ_C	300	13	299	99.7
	LIQPOOL	898	31	896	99.8
	LYO	299	9	297	99.3
Total	LIQ_A	595	22	594	99.8
	LIQ_B	603	13	603	100
	LIQ_C	600	19	599	99.8
	LIQPOOL	1798	54	1796	99.9
	LYO	599	15	596	99.5

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
SS = Symptom sheets used for the collection of solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100
Doses not according to protocol = number of doses with regurgitation or vomiting

Template 18 Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) reported during the 8-day (Day 0 to Day 7) follow-up period - Exposed Set

		Any symptom				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	LIQ_A	298	251	84.2	79.6	88.2
	LIQ_B	302	267	88.4	84.3	91.8
	LIQ_C	300	247	82.3	77.5	86.5
	LIQPOOL	900	765	85.0	82.5	87.3
	LYO	300	249	83.0	78.3	87.1
Dose 2	LIQ_A	297	247	83.2	78.4	87.2
	LIQ_B	301	260	86.4	82.0	90.0
	LIQ_C	300	236	78.7	73.6	83.2
	LIQPOOL	898	743	82.7	80.1	85.2
	LYO	299	247	82.6	77.8	86.7
Overall/dose	LIQ_A	595	498	83.7	80.5	86.6
	LIQ_B	603	527	87.4	84.5	89.9
	LIQ_C	600	483	80.5	77.1	83.6
	LIQPOOL	1798	1508	83.9	82.1	85.5
	LYO	599	496	82.8	79.5	85.7
Overall/subject	LIQ_A	298	283	95.0	91.8	97.2
	LIQ_B	302	287	95.0	91.9	97.2
	LIQ_C	300	275	91.7	87.9	94.5
	LIQPOOL	900	845	93.9	92.1	95.4
	LYO	300	279	93.0	89.5	95.6

LIQ_A = HRV vaccine liquid formulation Lot A LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
For each dose:
N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by at least one symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 19 Percentage of subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, after each dose of the HRV lyophilised and HRV PCV-free liquid vaccine for all groups. - Exposed Set

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Cough/runny nose	All	298	72	24.2	19.4	29.4	302	90	29.8	24.7	35.3	300	71	23.7	19.0	28.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	62	20.8	16.3	25.9	302	76	25.2	20.4	30.5	300	49	16.3	12.3	21.0
Diarrhoea	All	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
	Grade 3	298	3	1.0	0.2	2.9	302	2	0.7	0.1	2.4	300	2	0.7	0.1	2.4
	Related	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
Fever(°C)	All	298	63	21.1	16.6	26.2	302	59	19.5	15.2	24.5	300	57	19.0	14.7	23.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	61	20.5	16.0	25.5	302	58	19.2	14.9	24.1	300	55	18.3	14.1	23.2
Irritability	All	298	213	71.5	66.0	76.5	302	225	74.5	69.2	79.3	300	191	63.7	57.9	69.1
	Grade 3	298	12	4.0	2.1	6.9	302	17	5.6	3.3	8.9	300	9	3.0	1.4	5.6
	Related	298	203	68.1	62.5	73.4	302	220	72.8	67.5	77.8	300	184	61.3	55.6	66.9
Loss of appetite	All	298	79	26.5	21.6	31.9	302	79	26.2	21.3	31.5	300	73	24.3	19.6	29.6
	Grade 3	298	0	0.0	0.0	1.2	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	75	25.2	20.3	30.5	302	78	25.8	21.0	31.2	300	67	22.3	17.7	27.5
Vomiting	All	298	47	15.8	11.8	20.4	302	45	14.9	11.1	19.4	300	44	14.7	10.9	19.2
	Grade 3	298	11	3.7	1.9	6.5	302	7	2.3	0.9	4.7	300	7	2.3	0.9	4.7
	Related	298	45	15.1	11.2	19.7	302	43	14.2	10.5	18.7	300	39	13.0	9.4	17.3
Dose 2																
Cough/runny nose	All	297	92	31.0	25.8	36.6	301	104	34.6	29.2	40.2	300	95	31.7	26.4	37.3
	Grade 3	297	2	0.7	0.1	2.4	301	2	0.7	0.1	2.4	300	4	1.3	0.4	3.4
	Related	297	79	26.6	21.7	32.0	301	84	27.9	22.9	33.3	300	79	26.3	21.4	31.7
Diarrhoea	All	297	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	300	12	4.0	2.1	6.9
	Grade 3	297	1	0.3	0.0	1.9	301	2	0.7	0.1	2.4	300	2	0.7	0.1	2.4
	Related	297	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	300	12	4.0	2.1	6.9
Fever(°C)	All	297	80	26.9	22.0	32.4	301	79	26.2	21.4	31.6	300	94	31.3	26.1	36.9
	Grade 3	297	2	0.7	0.1	2.4	301	1	0.3	0.0	1.8	300	1	0.3	0.0	1.8
	Related	297	79	26.6	21.7	32.0	301	76	25.2	20.4	30.6	300	91	30.3	25.2	35.9
Irritability	All	297	201	67.7	62.0	73.0	301	224	74.4	69.1	79.3	300	202	67.3	61.7	72.6
	Grade 3	297	11	3.7	1.9	6.5	301	18	6.0	3.6	9.3	300	14	4.7	2.6	7.7
	Related	297	195	65.7	60.0	71.0	301	220	73.1	67.7	78.0	300	200	66.7	61.0	72.0
Loss of appetite	All	297	69	23.2	18.5	28.5	301	63	20.9	16.5	26.0	300	70	23.3	18.7	28.5
	Grade 3	297	1	0.3	0.0	1.9	301	0	0.0	0.0	1.2	300	0	0.0	0.0	1.2

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
	Related	297	67	22.6	17.9	27.7	301	59	19.6	15.3	24.5	300	68	22.7	18.1	27.8
Vomiting	All	297	43	14.5	10.7	19.0	301	40	13.3	9.7	17.7	300	33	11.0	7.7	15.1
	Grade 3	297	7	2.4	1.0	4.8	301	8	2.7	1.2	5.2	300	8	2.7	1.2	5.2
	Related	297	40	13.5	9.8	17.9	301	40	13.3	9.7	17.7	300	32	10.7	7.4	14.7

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 20 Percentage of subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, for each dose in the pooled HRV PCV-free liquid vaccine group and the HRV vaccine lyophilised formulation group - Exposed Set

		LIQPOOL					LYO				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/runny nose	All	900	233	25.9	23.1	28.9	300	79	26.3	21.4	31.7
	Grade 3	900	2	0.2	0.0	0.8	300	4	1.3	0.4	3.4
	Related	900	187	20.8	18.2	23.6	300	64	21.3	16.8	26.4
Diarrhoea	All	900	25	2.8	1.8	4.1	300	4	1.3	0.4	3.4
	Grade 3	900	7	0.8	0.3	1.6	300	1	0.3	0.0	1.8
	Related	900	25	2.8	1.8	4.1	300	3	1.0	0.2	2.9
Fever(°C)	All	900	179	19.9	17.3	22.6	300	68	22.7	18.1	27.8
	Grade 3	900	2	0.2	0.0	0.8	300	0	0.0	0.0	1.2
	Related	900	174	19.3	16.8	22.1	300	67	22.3	17.7	27.5
Irritability	All	900	629	69.9	66.8	72.9	300	207	69.0	63.4	74.2
	Grade 3	900	38	4.2	3.0	5.7	300	12	4.0	2.1	6.9
	Related	900	607	67.4	64.3	70.5	300	201	67.0	61.4	72.3
Loss of appetite	All	900	231	25.7	22.8	28.7	300	67	22.3	17.7	27.5
	Grade 3	900	1	0.1	0.0	0.6	300	1	0.3	0.0	1.8
	Related	900	220	24.4	21.7	27.4	300	63	21.0	16.5	26.1
Vomiting	All	900	136	15.1	12.8	17.6	300	55	18.3	14.1	23.2
	Grade 3	900	25	2.8	1.8	4.1	300	11	3.7	1.8	6.5
	Related	900	127	14.1	11.9	16.6	300	51	17.0	12.9	21.7
Dose 2											
Cough/runny nose	All	898	291	32.4	29.4	35.6	299	109	36.5	31.0	42.2
	Grade 3	898	8	0.9	0.4	1.7	299	2	0.7	0.1	2.4
	Related	898	242	26.9	24.1	30.0	299	89	29.8	24.6	35.3
Diarrhoea	All	898	22	2.4	1.5	3.7	299	8	2.7	1.2	5.2
	Grade 3	898	5	0.6	0.2	1.3	299	3	1.0	0.2	2.9
	Related	898	22	2.4	1.5	3.7	299	8	2.7	1.2	5.2
Fever(°C)	All	898	253	28.2	25.3	31.2	299	74	24.7	20.0	30.0
	Grade 3	898	4	0.4	0.1	1.1	299	3	1.0	0.2	2.9
	Related	898	246	27.4	24.5	30.4	299	71	23.7	19.0	29.0
Irritability	All	898	627	69.8	66.7	72.8	299	200	66.9	61.2	72.2
	Grade 3	898	43	4.8	3.5	6.4	299	12	4.0	2.1	6.9
	Related	898	615	68.5	65.3	71.5	299	196	65.6	59.9	70.9
Loss of appetite	All	898	202	22.5	19.8	25.4	299	62	20.7	16.3	25.8
	Grade 3	898	1	0.1	0.0	0.6	299	0	0.0	0.0	1.2
	Related	898	194	21.6	19.0	24.4	299	60	20.1	15.7	25.1
Vomiting	All	898	116	12.9	10.8	15.3	299	41	13.7	10.0	18.1
	Grade 3	898	23	2.6	1.6	3.8	299	11	3.7	1.9	6.5
	Related	898	112	12.5	10.4	14.8	299	40	13.4	9.7	17.8

LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 21 Percentage of doses and subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, after each dose of the HRV lyophilised and HRV PCV-free HRV liquid vaccine for all groups. - Exposed Set

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose																
Cough/runny nose	All	595	164	27.6	24.0	31.3	603	194	32.2	28.5	36.1	600	166	27.7	24.1	31.4
	Grade 3	595	3	0.5	0.1	1.5	603	2	0.3	0.0	1.2	600	5	0.8	0.3	1.9
	Related	595	141	23.7	20.3	27.3	603	160	26.5	23.0	30.3	600	128	21.3	18.1	24.8
Diarrhoea	All	595	11	1.8	0.9	3.3	603	16	2.7	1.5	4.3	600	20	3.3	2.0	5.1
	Grade 3	595	4	0.7	0.2	1.7	603	4	0.7	0.2	1.7	600	4	0.7	0.2	1.7
	Related	595	11	1.8	0.9	3.3	603	16	2.7	1.5	4.3	600	20	3.3	2.0	5.1
Fever(°C)	All	595	143	24.0	20.7	27.7	603	138	22.9	19.6	26.4	600	151	25.2	21.7	28.8
	Grade 3	595	3	0.5	0.1	1.5	603	1	0.2	0.0	0.9	600	2	0.3	0.0	1.2
	Related	595	140	23.5	20.2	27.1	603	134	22.2	19.0	25.8	600	146	24.3	21.0	28.0
Irritability	All	595	414	69.6	65.7	73.3	603	449	74.5	70.8	77.9	600	393	65.5	61.5	69.3
	Grade 3	595	23	3.9	2.5	5.7	603	35	5.8	4.1	8.0	600	23	3.8	2.4	5.7
	Related	595	398	66.9	62.9	70.7	603	440	73.0	69.2	76.5	600	384	64.0	60.0	67.8
Loss of appetite	All	595	148	24.9	21.4	28.6	603	142	23.5	20.2	27.1	600	143	23.8	20.5	27.4
	Grade 3	595	1	0.2	0.0	0.9	603	0	0.0	0.0	0.6	600	1	0.2	0.0	0.9
	Related	595	142	23.9	20.5	27.5	603	137	22.7	19.4	26.3	600	135	22.5	19.2	26.1
Vomiting	All	595	90	15.1	12.3	18.3	603	85	14.1	11.4	17.1	600	77	12.8	10.3	15.8
	Grade 3	595	18	3.0	1.8	4.7	603	15	2.5	1.4	4.1	600	15	2.5	1.4	4.1
	Related	595	85	14.3	11.6	17.4	603	83	13.8	11.1	16.8	600	71	11.8	9.4	14.7
Overall/subject																
Cough/runny nose	All	298	134	45.0	39.2	50.8	302	147	48.7	42.9	54.5	300	132	44.0	38.3	49.8
	Grade 3	298	3	1.0	0.2	2.9	302	2	0.7	0.1	2.4	300	5	1.7	0.5	3.8
	Related	298	118	39.6	34.0	45.4	302	125	41.4	35.8	47.2	300	108	36.0	30.6	41.7
Diarrhoea	All	298	11	3.7	1.9	6.5	302	15	5.0	2.8	8.1	300	19	6.3	3.9	9.7
	Grade 3	298	4	1.3	0.4	3.4	302	4	1.3	0.4	3.4	300	3	1.0	0.2	2.9
	Related	298	11	3.7	1.9	6.5	302	15	5.0	2.8	8.1	300	19	6.3	3.9	9.7
Fever(°C)	All	298	111	37.2	31.7	43.0	302	104	34.4	29.1	40.1	300	122	40.7	35.1	46.5
	Grade 3	298	3	1.0	0.2	2.9	302	1	0.3	0.0	1.8	300	2	0.7	0.1	2.4
	Related	298	109	36.6	31.1	42.3	302	100	33.1	27.8	38.7	300	118	39.3	33.8	45.1
Irritability	All	298	254	85.2	80.7	89.1	302	267	88.4	84.3	91.8	300	240	80.0	75.0	84.4
	Grade 3	298	20	6.7	4.1	10.2	302	31	10.3	7.1	14.3	300	21	7.0	4.4	10.5
	Related	298	252	84.6	80.0	88.5	302	265	87.7	83.5	91.2	300	238	79.3	74.3	83.8
Loss of appetite	All	298	111	37.2	31.7	43.0	302	113	37.4	31.9	43.1	300	111	37.0	31.5	42.7
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	106	35.6	30.1	41.3	302	108	35.8	30.4	41.5	300	109	36.3	30.9	42.1
Vomiting	All	298	70	23.5	18.8	28.7	302	59	19.5	15.2	24.5	300	61	20.3	15.9	25.3
	Grade 3	298	18	6.0	3.6	9.4	302	12	4.0	2.1	6.8	300	12	4.0	2.1	6.9
	Related	298	69	23.2	18.5	28.4	302	58	19.2	14.9	24.1	300	58	19.3	15.0	24.3

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by the specified symptom
For overall/subject:

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the specified symptom
All = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 22 Percentage of subjects with unsolicited symptoms classified by MedDRA SOC and PT from Day 0 to Day 30 after any vaccination in each HRV PCV-free vaccine liquid group - Exposed Set

Primary System Organ Class (CODE)	Preferred Term (CODE)	LIQ_A N = 298				LIQ_B N = 302				LIQ_C N = 300			
				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		24	8.1	5.2	11.7	26	8.6	5.7	12.4	33	11.0	7.7	15.1
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	1	0.3	0.0	1.8
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	1.2	2	0.7	0.1	2.4	1	0.3	0.0	1.8
	Flatulence (10016766)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	2	0.7	0.1	2.4
General disorders and administration site conditions (10018065)	Injection site erythema (10022061)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Injection site pain (10022086)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Injection site swelling (10053425)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Irritability (10022998)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	1	0.3	0.0	1.8
	Pyrexia (10037660)	4	1.3	0.4	3.4	3	1.0	0.2	2.9	4	1.3	0.4	3.4
Immune system disorders (10021428)	Hypersensitivity (10020751)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
Infections and infestations (10021881)	Bronchitis (10006451)	2	0.7	0.1	2.4	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Ear infection (10014011)	1	0.3	0.0	1.9	3	1.0	0.2	2.9	2	0.7	0.1	2.4
	Exanthema subitum (10015586)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Eye infection (10015929)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Gastroenteritis (10017888)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Impetigo (10021531)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Influenza (10022000)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Laryngitis (10023874)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Otitis media (10033078)	5	1.7	0.5	3.9	6	2.0	0.7	4.3	11	3.7	1.8	6.5
	Perianal abscess (10034447)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2

Primary System Organ Class (CODE)	Preferred Term (CODE)	LIQ_A N = 298				LIQ_B N = 302				LIQ_C N = 300			
				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pneumonia (10035664)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Respiratory tract infection (10062352)	3	1.0	0.2	2.9	2	0.7	0.1	2.4	0	0.0	0.0	1.2
	Respiratory tract infection viral (10062106)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rhinitis (10039083)	2	0.7	0.1	2.4	1	0.3	0.0	1.8	3	1.0	0.2	2.9
	Upper respiratory tract infection (10046306)	2	0.7	0.1	2.4	5	1.7	0.5	3.8	7	2.3	0.9	4.7
	Varicella (10046980)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	2	0.7	0.1	2.4
Psychiatric disorders (10037175)	Crying (10011469)	0	0.0	0.0	1.2	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	1.9	1	0.3	0.0	1.8	6	2.0	0.7	4.3
	Nasal congestion (10028735)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Rales (10037833)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Eczema (10014184)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rash (10037844)	2	0.7	0.1	2.4	0	0.0	0.0	1.2	0	0.0	0.0	1.2

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the MedDRA PT
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 23 Percentage of doses with unsolicited symptoms classified by MedDRA SOC and PT from Day 0 to Day 30 after vaccination in each HRV PCV-free liquid vaccine group - Exposed Set

		LIQ_A N = 595				LIQ_B N = 603				LIQ_C N = 600			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		25	4.2	2.7	6.1	30	5.0	3.4	7.0	38	6.3	4.5	8.6
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	1	0.2	0.0	0.9
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	0.6	2	0.3	0.0	1.2	1	0.2	0.0	0.9
	Flatulence (10016766)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	2	0.3	0.0	1.2
General disorders and administration site conditions (10018065)	Injection site erythema (10022061)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Injection site pain (10022086)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Injection site swelling (10053425)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Irritability (10022998)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.2	0.0	0.9
	Pyrexia (10037660)	4	0.7	0.2	1.7	3	0.5	0.1	1.4	4	0.7	0.2	1.7
Immune system disorders (10021428)	Hypersensitivity (10020751)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Infections and infestations (10021881)	Bronchitis (10006451)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Ear infection (10014011)	1	0.2	0.0	0.9	3	0.5	0.1	1.4	2	0.3	0.0	1.2
	Exanthema subitum (10015586)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Eye infection (10015929)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Gastroenteritis (10017888)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Impetigo (10021531)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Influenza (10022000)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Laryngitis (10023874)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Otitis media (10033078)	6	1.0	0.4	2.2	7	1.2	0.5	2.4	12	2.0	1.0	3.5
	Perianal abscess (10034447)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Pneumonia (10035664)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Respiratory tract infection (10062352)	3	0.5	0.1	1.5	2	0.3	0.0	1.2	0	0.0	0.0	0.6
	Respiratory tract infection viral (10062106)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Rhinitis (10039083)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.5	0.1	1.5
	Upper respiratory tract infection (10046306)	2	0.3	0.0	1.2	6	1.0	0.4	2.2	8	1.3	0.6	2.6
	Varicella (10046980)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	2	0.3	0.0	1.2

		LIQ_A N = 595				LIQ_B N = 603				LIQ_C N = 600			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Psychiatric disorders (10037175)	Crying (10011469)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
Respiratory, thoracic and mediastinal disorders	Cough (10011224)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	6	1.0	0.4	2.2
(10038738)	Nasal congestion (10028735)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Rales (10037833)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Eczema (10014184)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Rash (10037844)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	0	0.0	0.0	0.6

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = Total number of doses administered
n/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the MedDRA PT
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit

Template 24 Percentage of subjects reporting any GE episodes from Dose 1 of HRV vaccine up to Visit 3 - Exposed Set

Group	Between Dose 1 and before Dose 2					Between Dose 2 and Visit 3					Between Dose 1 and Visit 3				
				95% CI					95% CI					95% CI	
	N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
LIQ_A	298	16	5.4	3.1	8.6	297	10	3.4	1.6	6.1	298	25	8.4	5.5	12.1
LIQ_B	302	17	5.6	3.3	8.9	301	15	5.0	2.8	8.1	302	29	9.6	6.5	13.5
LIQ_C	300	17	5.7	3.3	8.9	300	18	6.0	3.6	9.3	300	33	11.0	7.7	15.1
LIQPOOL	900	50	5.6	4.2	7.3	898	43	4.8	3.5	6.4	900	87	9.7	7.8	11.8
LYO	300	8	2.7	1.2	5.2	299	15	5.0	2.8	8.1	300	22	7.3	4.7	10.9

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
Between Dose 1 and before Dose 2: N = number of subjects having received the first dose
Between Dose 2 and Visit 3: N = number of subjects having received the second dose
Between Dose 1 and Visit 3: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one gastroenteritis episode during the specified period
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 25 Percentage of subjects reporting RV (vaccine strain or wild type RV) GE episodes from Dose 1 of HRV vaccine up to Visit 3 - Exposed Set

Group	Between Dose 1 and before Dose 2					Between Dose 2 and Visit 3					Between Dose 1 and Visit 3				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
LIQ_A	298	0	0.0	0.0	1.2	297	0	0.0	0.0	1.2	298	0	0.0	0.0	1.2
LIQ_B	302	1	0.3	0.0	1.8	301	0	0.0	0.0	1.2	302	1	0.3	0.0	1.8
LIQ_C	300	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8	300	1	0.3	0.0	1.8
LIQPOOL	900	1	0.1	0.0	0.6	898	1	0.1	0.0	0.6	900	2	0.2	0.0	0.8
LYO	300	0	0.0	0.0	1.2	299	0	0.0	0.0	1.2	300	0	0.0	0.0	1.2

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
LIQPOOL = Pooled HRV vaccine liquid formulation
LYO = HRV vaccine lyophilised formulation
Between Dose 1 and before Dose 2: N = number of subjects having received the first dose
Between Dose 2 and Visit 3: N = number of subjects having received the second dose
Between Dose 1 and Visit 3: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one RV GE episode during the specified period
95% CI = exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

Template 26 Summary of RV GE episodes reported from Dose 1 of HRV vaccine up to Visit 3 - Exposed Set

Subject no	Onset of episode	Isolated RV type
PP C	Day 3 of Dose 1	G1/P8 vaccine strain
PP D	Day 23 of Dose 2	G1/P8 vaccine strain

Template 27 Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 7 after vaccination by type in each HRV PCV-free vaccine liquid group - Exposed Set

	LIQ_A					LIQ_B					LIQ_C				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1															
Any	298	173	58.1	52.2	63.7	302	175	57.9	52.2	63.6	300	157	52.3	46.5	58.1
Any antipyretic	298	97	32.6	27.3	38.2	302	94	31.1	25.9	36.7	300	71	23.7	19.0	28.9
Prophylactic antipyretic	298	8	2.7	1.2	5.2	302	6	2.0	0.7	4.3	300	9	3.0	1.4	5.6
Any antibiotic	298	6	2.0	0.7	4.3	302	5	1.7	0.5	3.8	300	5	1.7	0.5	3.8
Dose 2															
Any	297	105	35.4	29.9	41.1	301	117	38.9	33.3	44.6	300	89	29.7	24.6	35.2
Any antipyretic	297	98	33.0	27.7	38.7	301	109	36.2	30.8	41.9	300	86	28.7	23.6	34.1
Prophylactic antipyretic	297	7	2.4	1.0	4.8	301	8	2.7	1.2	5.2	300	6	2.0	0.7	4.3
Any antibiotic	297	4	1.3	0.4	3.4	301	8	2.7	1.2	5.2	300	4	1.3	0.4	3.4
Overall/dose															
Any	595	278	46.7	42.7	50.8	603	292	48.4	44.4	52.5	600	246	41.0	37.0	45.1
Any antipyretic	595	195	32.8	29.0	36.7	603	203	33.7	29.9	37.6	600	157	26.2	22.7	29.9
Prophylactic antipyretic	595	15	2.5	1.4	4.1	603	14	2.3	1.3	3.9	600	15	2.5	1.4	4.1
Any antibiotic	595	10	1.7	0.8	3.1	603	13	2.2	1.2	3.7	600	9	1.5	0.7	2.8
Overall/subject															
Any	298	194	65.1	59.4	70.5	302	205	67.9	62.3	73.1	300	182	60.7	54.9	66.2
Any antipyretic	298	130	43.6	37.9	49.5	302	141	46.7	41.0	52.5	300	111	37.0	31.5	42.7
Prophylactic antipyretic	298	11	3.7	1.9	6.5	302	12	4.0	2.1	6.8	300	13	4.3	2.3	7.3
Any antibiotic	298	10	3.4	1.6	6.1	302	13	4.3	2.3	7.2	300	9	3.0	1.4	5.6

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
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

Template 28 Percentage of subjects reporting each solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 0 to Day 7) follow-up period, for each documented dose in each HRV PCV-free liquid group - Exposed Set

		LIQ_A					LIQ_B					LIQ_C				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1																
Cough/runny nose	All	298	72	24.2	19.4	29.4	302	90	29.8	24.7	35.3	300	71	23.7	19.0	28.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	62	20.8	16.3	25.9	302	76	25.2	20.4	30.5	300	49	16.3	12.3	21.0
Diarrhoea	All	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
	Grade 3	298	3	1.0	0.2	2.9	302	2	0.7	0.1	2.4	300	2	0.7	0.1	2.4
	Related	298	8	2.7	1.2	5.2	302	9	3.0	1.4	5.6	300	8	2.7	1.2	5.2
Fever(°C)	All	298	63	21.1	16.6	26.2	302	59	19.5	15.2	24.5	300	57	19.0	14.7	23.9
	Grade 3	298	1	0.3	0.0	1.9	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	61	20.5	16.0	25.5	302	58	19.2	14.9	24.1	300	55	18.3	14.1	23.2
Irritability	All	298	213	71.5	66.0	76.5	302	225	74.5	69.2	79.3	300	191	63.7	57.9	69.1
	Grade 3	298	12	4.0	2.1	6.9	302	17	5.6	3.3	8.9	300	9	3.0	1.4	5.6
	Related	298	203	68.1	62.5	73.4	302	220	72.8	67.5	77.8	300	184	61.3	55.6	66.9
Loss of appetite	All	298	79	26.5	21.6	31.9	302	79	26.2	21.3	31.5	300	73	24.3	19.6	29.6
	Grade 3	298	0	0.0	0.0	1.2	302	0	0.0	0.0	1.2	300	1	0.3	0.0	1.8
	Related	298	75	25.2	20.3	30.5	302	78	25.8	21.0	31.2	300	67	22.3	17.7	27.5
Vomiting	All	298	47	15.8	11.8	20.4	302	45	14.9	11.1	19.4	300	44	14.7	10.9	19.2
	Grade 3	298	11	3.7	1.9	6.5	302	7	2.3	0.9	4.7	300	7	2.3	0.9	4.7
	Related	298	45	15.1	11.2	19.7	302	43	14.2	10.5	18.7	300	39	13.0	9.4	17.3
Dose 2																
Cough/runny nose	All	296	92	31.1	25.9	36.7	301	104	34.6	29.2	40.2	299	95	31.8	26.5	37.4
	Grade 3	296	2	0.7	0.1	2.4	301	2	0.7	0.1	2.4	299	4	1.3	0.4	3.4
	Related	296	79	26.7	21.7	32.1	301	84	27.9	22.9	33.3	299	79	26.4	21.5	31.8
Diarrhoea	All	296	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	299	12	4.0	2.1	6.9
	Grade 3	296	1	0.3	0.0	1.9	301	2	0.7	0.1	2.4	299	2	0.7	0.1	2.4
	Related	296	3	1.0	0.2	2.9	301	7	2.3	0.9	4.7	299	12	4.0	2.1	6.9
Fever(°C)	All	296	80	27.0	22.1	32.5	301	79	26.2	21.4	31.6	299	94	31.4	26.2	37.0
	Grade 3	296	2	0.7	0.1	2.4	301	1	0.3	0.0	1.8	299	1	0.3	0.0	1.8
	Related	296	79	26.7	21.7	32.1	301	76	25.2	20.4	30.6	299	91	30.4	25.3	36.0
Irritability	All	296	201	67.9	62.3	73.2	301	224	74.4	69.1	79.3	299	202	67.6	61.9	72.8
	Grade 3	296	11	3.7	1.9	6.6	301	18	6.0	3.6	9.3	299	14	4.7	2.6	7.7
	Related	296	195	65.9	60.2	71.3	301	220	73.1	67.7	78.0	299	200	66.9	61.2	72.2
Loss of appetite	All	296	69	23.3	18.6	28.6	301	63	20.9	16.5	26.0	299	70	23.4	18.7	28.6
	Grade 3	296	1	0.3	0.0	1.9	301	0	0.0	0.0	1.2	299	0	0.0	0.0	1.2
	Related	296	67	22.6	18.0	27.8	301	59	19.6	15.3	24.5	299	68	22.7	18.1	27.9
Vomiting	All	296	43	14.5	10.7	19.1	301	40	13.3	9.7	17.7	299	33	11.0	7.7	15.1
	Grade 3	296	7	2.4	1.0	4.8	301	8	2.7	1.2	5.2	299	8	2.7	1.2	5.2
	Related	296	40	13.5	9.8	17.9	301	40	13.3	9.7	17.7	299	32	10.7	7.4	14.8

LIQ_A = HRV vaccine liquid formulation Lot A
LIQ_B = HRV vaccine liquid formulation Lot B
LIQ_C = HRV vaccine liquid formulation Lot C
N = number of subjects with the considered documented dose
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
95% CI = Exact 95% Confidence Interval; LL = Lower Limit, UL = Upper Limit
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination

Template 29 Listing of dropouts due to AEs, SAEs and solicited symptoms (Total cohort)

Study-Subject No.	Country	Gender	AE Description	SAE	Causality	Outcome	Type of discontinuation
PPD	Germany	F	SUBJECT DIED	Y		Fatal	Study at visit/contact: VISIT11 (Y5)
PPD	Germany	F	SUBJECT DIED	Y		Fatal	Study at visit/contact: VISIT11 (Y5)

Template 30 Subjects with Serious Adverse Events reported up to Visit 3 - Exposed Set

Sub. No.	Country	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
PP	US	PP	M	Kawasaki's disease	Kawasaki's disease	Infections and infestations	HO	1	12	29	N	Recovered/resolved

MA = medical attention
HO = hospitalisation
Dose = dose given prior to the start of the SAE
Day of onset = number of days since last study vaccine dose

Template 31 Number (%) of subjects with serious adverse events from Dose 1 up to study end, including number of events reported (Exposed Set)

			Gr 1 N =			Gr2 N =		
Type of Event	Primary System Organ Class	Preferred Term (CODE)	n*	n	%	n*	n	%
SAE	At least one symptom							
	<each SOC>	<each PT term>						
Related SAE	At least one symptom							
	<each SOC>	<each PT term>						
Fatal SAE	At least one symptom							
	<each SOC>	<each PT term>						
Related fatal SAE	At least one symptom							
	<each SOC>	<each PT term>						

Gr 1 = Group 1 description
Gr 2 = Group 2 description
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 32 Solicited and unsolicited symptoms experienced by at least 5 % of subjects classified by MedDRA Primary System Organ Class and Preferred Term within 31-day (Days 0-30) post-vaccination period after any dose of HRV PCV-free liquid vaccine - SAE excluded (Exposed Set)

		HPV_2D N =			MMR_DTPa N =		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
At least one symptom							
<each SOC>	<each PT term>						

HPV_2D = females aged 4-6 years who received two doses of HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
MMR_DTPa = females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 33 Number of subjects by country

	ACWY-TT N = 259	**ACWYHPV N = 259**	**HPV N = 261**	**Co-ad N = 260**	**Tdap N = 261**	**Total N = 1300**
Country	**n**	**n**	**N**	**n**	**n**	**n**
Dominican Republic	86	87	88	87	87	435
Estonia	87	86	87	87	88	435
Thailand	86	86	86	86	86	430

ACWY-TT = Subjects who received MenACWY-TT at Month 0 and Cervarix at Month 1, 2 and 7
ACWYHPV = Subjects who received MenACWY-TT and Cervarix at Month 0 and Cervarix at Month 1 and 6
HPV = Subjects who received Cervarix at Month 0, 1 and 6
Co-ad = Subjects who received MenACWY-TT, Cervarix and Boostrix at Month 0 and Cervarix at Month 1 and 6
Tdap = Subjects who received Boostrix and Cervarix at Month 0 and Cervarix at Month 1 and 6
N = number of subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories

Template 34 Number of enrolled subjects by age category (Exposed Set)

		Gr 1 N =	Gr 2 N =	Gr 3 N =	Total N =
Characteristics	**Categories**	**n**	**n**	**n**	**n**
Age category	In utero				
	Preterm newborn infants (gestational age < 37 wks)				
	Newborns (0-27 days)				
	Infants and toddlers (28 days-23 months)				
	Children (2-11 years)				
	Adolescents (12-17 years)				
	Adults (18-64 years)				
	From 65-84 years				
	85 years and over				
	Missing				

Gr 1 = Group 1 description
Gr 2 = Group 2 description
Gr 3 = Group 3 description
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories
Missing = <describe missing>

Template 35 Study population (Exposed Set)

Number of subjects	[each group]	Total
Planned, N		
Randomised, N (<Total Vaccinated Cohort>)		
Completed, n (%)		
Demographics		
N (<Total Vaccinated Cohort>)		
Females:Males		
Mean Age, <years> (SD)		
Median Age, <years> (minimum, maximum)		
<Most frequent category of race>, n (%)		
<Second most frequent category of race>, n (%)		
<Third most frequent category of race>, n (%)		

[each group]:
Short group label= long group label