GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase IIIA, randomized, single-blind, multi-centric study to evaluate the immunogenicity, reactogenicity and safety of three doses of Pediarix®, Hiberix® and Prevenar 13® when co-administered with two doses of the PCV-free liquid formulation of GSK Biologicals' oral live attenuated HRV vaccine as compared to the currently licensed lyophilized formulation of the HRV vaccine in healthy infants 6-12 weeks of age.
eTrack study number and Abbreviated Title	201663 (ROTA-090)
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	01-Aug-2017 Final
Co-ordinating author:	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 (Scientific writer) PPD (Regulatory Affair) PPD (Clinical Safety representative) PPD (Public Disclosure representative)
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: 14April 2017)

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LIST OF ABBREVIATIONS

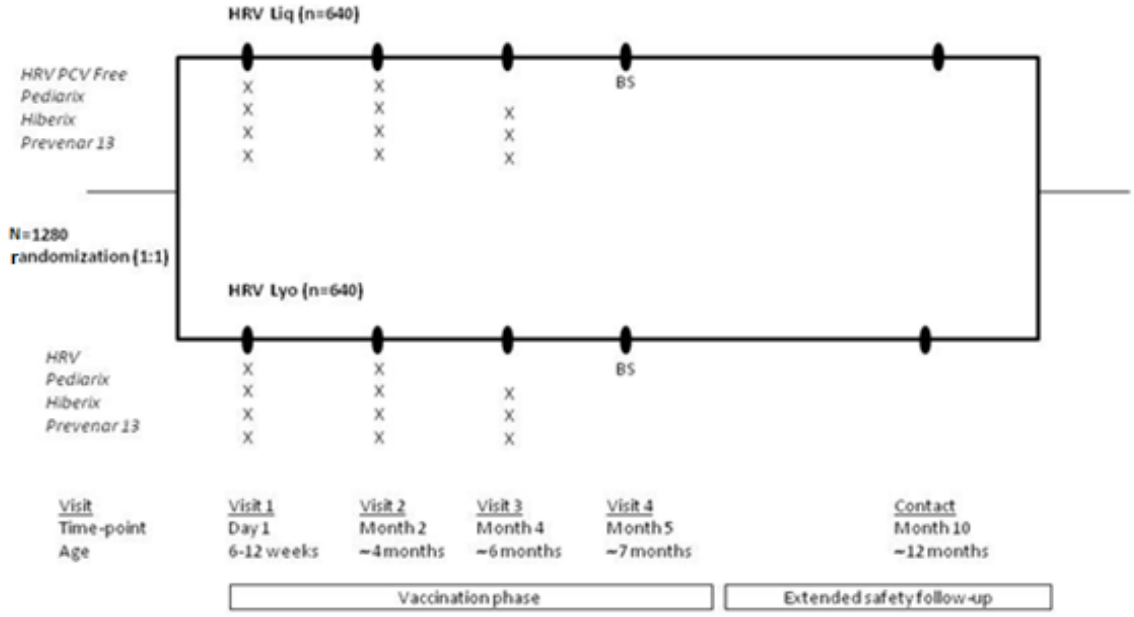
AE	Adverse event
ANOVA	Analysis of Variance
cDISCI	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EL.U/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent 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
01-AUG-2017	first version	Final – 27-OCT-2016

2. STUDY DESIGN



N = Number of subjects planned to be enrolled, **n** = Number of subjects in each study group, **BS** = blood sample.
Contact (by telephone call or any other convenient procedure) will take place 6 months after Visit 3 for safety follow-up.
An IDMC will review the safety data by treatment group periodically. Details of the review will be described in an IDMC charter

Protocol waivers or exemptions are not allowed unless necessary for the management 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, single-blind, randomized, controlled, multi-centric study with two parallel groups.
- Duration of the study: The total duration of the study, per subject, will be approximately 10 months including the 6 months of Extended Safety Follow-Up (ESFU) period after the last dose of study vaccine administered.
  - Epoch 001: Primary starting at Visit 1 (Day 1) and ending at the ESFU contact (Month 10).
- Primary completion Date (PCD): Last subject attending Visit 4.

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released for samples collected at Visit 4. If the last testing results are available before the Last Subject Last Visit (LSLV), i.e., before the ESFU, the EoS will then be the LSLV.

Refer to glossary of terms for the definition of EoS.

The study groups and the 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 001
HRV Liq	640	6 weeks-12 weeks	●
HRV Lyo	640	6 weeks-12 weeks	●

The study groups and the treatment planned for the study are provided in Table 2.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		HRV Liq	HRV Lyo
HRV Liquid	HRV PCV-free	X	
HRV Lyophilized	HRV*		x
Pediarix	DTPa-HBV-IPV	X	x
Hiberix	*Hib*	X	x
Prevenar 13	*Prevenar 13*	X	x

*Licensed lyophilized HRV vaccine.

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

- Vaccination schedule: Two doses of HRV vaccine to be administered according to a 0, 2 month schedule as per the immunization schedule for HRV vaccine administration in the US.

  Co-administration of routine childhood vaccines *Pediarix*, *Hiberix* and *Prevenar 13* will be performed as follows:

  – All the subjects will receive a dose each of *Pediarix*, *Hiberix* and *Prevenar 13* at Visit 1 (Day 1), Visit 2 (Month 2) and Visit 3 (Month 4).

  – The routine booster dose for the co-administered vaccines will not be administered to subjects as a part of this study. Subject's parent(s)/LARs will be reminded at Visit 4 to consult their primary health care provider regarding the booster dose of the vaccines for their child.

- Treatment allocation: Randomized 1:1 using GSK Biologicals' Randomization System on Internet (SBIR).

- Blinding: single-blind

The blinding of the study epoch is provided in Table 3.

Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	single-blind

- Sampling schedule: Details of the samples to be collected are as follows:
  - Blood samples will be collected from all subjects at Visit 4 (Month 5) to measure serum anti-RV IgA antibody concentrations and antibody concentrations/titers against all the antigens in the co-administered vaccines.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: An IDMC consisting of clinical experts and a biostatistician will review the safety data by treatment group periodically to monitor the safety aspects of the PCV-free liquid HRV vaccine.

3. OBJECTIVES

3.1. Primary objectives

- To demonstrate the non-inferiority of the immune responses to three doses of *Pediarix, Hiberix* and *Prevenar* 13 when co-administered with two doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with the currently licensed lyophilized HRV vaccine, 1 month after Dose 3 of routine infant vaccines.

Criteria for non-inferiority:

- *Lower limits of the two-sided standardized asymptotic 95% confidence intervals (CIs) on the differences between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with seroprotective concentrations (≥0.1 IU/mL) for each of anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibodies are ≥-10% (clinical limit for non-inferiority),*
- *The lower limit of the two-sided standardized asymptotic 95% CI on the difference between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with seroprotective concentration (≥10 mIU/mL) for antibodies against hepatitis B surface antigen (anti-HBs) is ≥-10% (clinical limit for non-inferiority),*
- *Lower limits of the two-sided standardized asymptotic 95% CIs on the differences between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with seroprotective titers (≥8 ED_{50}) for each of anti-poliovirus serotypes 1, 2 and 3 antibodies are ≥-5% (clinical limit for non-inferiority),*

- *Lower limits of the two-sided 95% CIs on the geometric mean antibody concentrations (GMC) ratios (HRV Liq group over HRV Lyo group) for antibodies against each of the pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN) antigens [anti-PT, anti-FHA and anti-PRN] are ≥0.67 (clinical limit for non-inferiority),*
- *Lower limits of the two-sided 95% CIs on the GMC ratios (HRV Liq group over HRV Lyo group) for each of the 13 Streptococcus pneumoniae (S. pneumoniae) serotypes are ≥0.5 (clinical limit for non-inferiority),*
- *The lower limit of the two-sided standardized asymptotic 95% CI on the difference between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with concentration of antibodies against polyribosyl-ribitol-phosphate antigen (anti-PRP) ≥0.15 μg/mL is ≥- 5%,*
- *The lower limit of the two-sided standardized asymptotic 95% CI on the difference between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with concentration of antibodies against anti-PRP ≥1.0 μg/mL is ≥-10% (clinical limit for non-inferiority).*

- To rule out a 10% decrease in seroresponse to PT, FHA and PRN antigen when *Pediarix* is co-administered with PCV-free-liquid HRV vaccine compared to when *Pediarix* is co-administered with the currently licensed lyophilized HRV vaccine.
  - seroresponse is defined as the percentage of subjects showing an antibody concentration above a threshold that leads to 95% seroresponse in the control group (lyophilized HRV vaccine),
  - p-value on the difference in seroresponse between groups is <2.5% for each PT, FHA and PRN antigen (p-value is computed by integrating on the p-value for the null hypothesis that the seroresponse rate in the liquid group is <85% and the a-posteriori probability of the threshold in the lyophilized group).

3.2. Secondary objectives

Immunogenicity:

- To assess the immunogenicity of the PCV-free liquid HRV vaccine and currently licensed lyophilized HRV vaccine in terms of serum anti-rotavirus immunoglobulin A (IgA) antibody seropositivity rate at Visit 4, 3 months after Dose 2 of the HRV vaccine.
- To assess the immunogenicity of routine infant vaccines *Pediarix*, *Hiberix* and *Prevenar* 13 when co-administered with the PCV-free liquid HRV vaccine and currently licensed lyophilized HRV vaccine at Visit 4, 1 month after Dose 3 of routine infant vaccines.

Reactogenicity and safety:

- To assess the reactogenicity of the PCV-free liquid HRV vaccine and currently licensed lyophilized HRV vaccine in terms of general solicited adverse events (AEs) during the 8 day (Day 1-Day 8) follow-up period after each dose of HRV vaccine.
- To assess the safety of the study vaccines in terms of unsolicited AEs during the 31 day (Day 1-Day 31) follow-up period after each dose of HRV vaccine and serious adverse events (SAEs) during the entire study period.

4. ENDPOINTS

4.1. Primary endpoints

- Immunogenicity with respect to components of the routine infant vaccines, one month after Dose 3 of routine infant vaccines (Visit 4):
  - Anti-D antibody concentration ≥0.1 IU/mL,
  - Anti-T antibody concentration ≥0.1 IU/mL,
  - Anti-HBs antibody concentrations ≥10 mIU/mL,
  - Anti-poliovirus types 1, 2 and 3 antibody titers ≥8 ED_{50},
  - Anti-PT, anti-FHA and anti-PRN antibody concentrations expressed as GMCs,
  - Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations expressed as GMCs,
  - Anti-PRP antibody concentrations ≥0.15 µg/mL,
  - Anti-PRP antibody concentrations ≥1.0 µg/mL.
- Difference in seroresponse with respect to PT, FHA and PRN antigen components one month after Dose 3 of routine infant vaccines (Visit 4):
  - Seroresponse to anti-PT, anti-FHA and anti-PRN.

4.2. Secondary endpoints

- Serum anti-rotavirus IgA antibody seropositivity 3 months after Dose 2 of HRV vaccine (Visit 4).
  - Serum anti-RV IgA antibody concentrations ≥20 U/mL and ≥90 U/mL 1-2 months after Dose 2.
- Immunogenicity with respect to components of the routine infant vaccines, one month after Dose 3 of routine infant vaccines (Visit 4):
  - PT, anti-FHA and anti-PRN antibody concentrations ≥2.693 IU/mL, ≥2.046 IU/mL and ≥2.187 IU/mL, respectively.
  - Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations ≥0.35 µg/mL for the ELISA,

  - Anti-D, anti-T, anti-PRP and anti-HBs antibody concentrations expressed as GMCs and anti-poliovirus types 1, 2 and 3 antibody concentrations expressed as Geometric Mean Titers (GMTs).

- Occurrence of general solicited AEs during the 8 day (Day 1-Day 8) follow-up period after each dose of HRV vaccine.
- Occurrence of unsolicited AEs within 31 days (Day 1-Day 31) after any dose of HRV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs from Dose 1 of study vaccines up to study end.

5. ANALYSIS SETS

All analyses will be performed per treatment actually administered at Dose 1.

5.1. Definition

5.1.1. Exposed Set

The Exposed Set (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 is available.

5.1.2. Per-protocol Set for analysis of immunogenicity (PPS)

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

- who have received the study vaccines according to their random assignment,
- who comply with the vaccination schedule of routine infant vaccines and HRV vaccines as per Table 5,
- for whom the routine infant vaccines were administered according to the protocol as per Table 4,
- for whom the HRV vaccine liquid or lyophilized formulation was administered according to protocol,
- who have not received a vaccine not specified or forbidden in the protocol up to Visit 4 blood sampling,
- who had not received medication forbidden by the protocol up to Visit 4 blood sampling,
- whose underlying medical condition(s) was (were) not forbidden by the protocol up to Visit 4 blood sample,

- for whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one routine infant vaccine antigen component,
- who comply with the blood sampling schedule after the 3rd dose of Pediarix, Hiberix and Prevenar 13 as per Table 5,
- who have no concomitant infection up to Visit 4 blood sample, which may influence the immune system.

Table 4 Dosage and administration

Type of contact and time-point	Study group	Treatment name	Volume to be administered	Route[1]	Site		
					Location	Directionality[2]	Laterality
Visit 1, Visit 2	HRV Liq	HRV Liquid	1.5 ml	O	Not applicable	Not applicable	Not applicable
Visit 1 , Visit 2	HRV Lyo	HRV Lyophilized	1 ml	O	Not applicable	Not applicable	Not applicable
Visit 1, Visit 2, Visit 3	HRV Liq, HRV Lyo	*Pediarix*	0.5 ml	IM	Thigh	Upper	Right
Visit 1, Visit 2, Visit 3	HRV Liq, HRV Lyo	*Hiberix*	0.5 ml	IM	Thigh	Anterolateral	Right
Visit 1, Visit 2, Visit 3	HRV Liq, HRV Lyo	*Prevenar 13*	0.5 ml	IM	Thigh	Lower	Left

[1]Oral (O), Intramuscular (IM)
[2] Directionality is a qualifier for further detailing the location of the vaccine administration.

Table 5 Maximum allowed interval between visits

Interval	Allowed length of interval
Visit 1→Visit 2	49 days-83 days after Dose 1 of study vaccines 1
Visit 2→Visit 3	56 days-83 days after Dose 2 of study vaccines 1
Visit 3 →Visit 4	21 days-48 days after Dose 3 of study vaccines 1
Visit 3 →ESFU	180 days-210 days after Dose 3 of study vaccines

[1] Subjects will not be eligible for inclusion in the Per-Protocol Set (PPS) for analysis of immunogenicity, if they make the study visit outside this interval. This is not applicable for the interval between Visit 3 and ESFU.

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each 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)

5.2.2.1. Excluded subjects

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 => Invalid informed consent or fraudulent data
1030	Study vaccine dose not administrated at all 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 during the period starting from 30 days before the first dose of study vaccine administration and ending at Visit 4 blood sampling, with the exception of the inactivated influenza vaccine
1060	Randomization code broken => Subjects unblinded in SBIR or unblinding reported as protocol deviation
1070	Study vaccine dose not administered according to protocol => • Subjects orally vaccinated with the correct vaccine but who regurgitated during the same visit, without replacement dose, • Route of vaccination which is not oral for HRV vaccines • Route of vaccination is not Intramuscular for Pediarix, Hiberix or Prevnar 13 • Incomplete vaccination course for HRV, Pediarix, Hiberix or Prevnar 13 regardless of dropout. • Pediarix, Hiberix or Prevnar 13 not administered on the same day as planned. • Wrong replacement or accidental receipt of wrong study vaccine (not compatible with study/randomized regimen) • Wrong reconstitution of administered vaccine
1080	Vaccine temperature deviation => vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090	Expired vaccine administered=> Subjects who received an expired vaccine
2010	Protocol violation (inclusion/exclusion criteria) => ineligible subject: • A male or female infant is not between 6 and 12 weeks (42-90 days) of gestational age at the time of the first study vaccination • Other considerations as stated in section 4.2 – 4.3 in the protocol

2040	Administration of any medication forbidden by the protocol:=> • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period between the first vaccination at Visit 1 to the blood sampling at Visit 4. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period between Visit 1 to Visit 4. 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 the first vaccination at Visit 1 to the blood sampling at Visit 4. • Administration of long-acting immune-modifying drugs between the first vaccination at Visit 1 to the blood sampling at Visit 4 (e.g., infliximab).
2070	Concomitant infection not related to the vaccine which may influence immune response = > who have concomitant infection up to Visit 4 blood sample, which may influence the immune system (GE episodes not to be considered).
2080	Non-compliance with vaccination schedule => Subjects that did not comply with the vaccination interval as stated in Table 5 (including wrong and unknown dates):
2090	Non-compliance with the blood sampling schedule (including wrong and unknown dates) => Blood sample not collected within 21 days-48 days after the third dose of the co-administered vaccines (Visit 4).
2100	Essential serological data missing => No serological results at all available post-vaccination
2120	Obvious incoherence or abnormality or error in data =>BS result available while BS not taken

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Not applicable

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

Important protocol deviations not leading to elimination from PPS for immunogenicity will be reported by groups. This includes but is not limited to

- 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.
- Short follow-up: subjects who completed the last study contact before the minimum length of follow-up requirement (180 days).
- HRV vaccination without documentation of solicited symptoms i.e. for a HRV vaccine dose administered, at least one solicited symptom is not documented as being present or absent.

The full list of reportable protocol deviations is available in the study protocol deviation management plan.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in annex 1 and will not be repeated below.

6.1. Demography

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

The median, mean, range and standard deviation of age (in weeks) at each study vaccine dose and of the gestational age will be computed by group. The median, mean and standard deviation of length (in centimeters) and weight (in kilograms) at Visit 1 will computed by group. The racial and sex composition of the subjects will be presented.

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

The number 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.

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. An analysis on the ES will be performed only if, in any group, more than 5% of the vaccinated subjects with immunological data are excluded from the PPS for immunogenicity.

6.3.1.1. Within group analysis

For each treatment group, one month after Dose 3 of routine infant vaccines at Visit 4 (Month 5) time-point:

- Seroprotection rates against HBsAg, diphtheria toxoid, tetanus toxoid, PRP antigen and poliovirus types 1, 2 and 3 (with exact 95% CI) will be calculated.
- Seropositivity rates and their exact 95% CIs for antibodies against PT, FHA, PRN, anti-rotavirus, S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and HBsAg will be tabulated.
- Percentage of subjects with anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations ≥0.35 µg/mL with 95% CI will be calculated.
- Percentage of subjects with anti-PRP antibody concentrations ≥1.0 µg/mL will be calculated with 95% CI.

- Percentage of subjects with anti RV IgA antibody concentration ≥90 U/mL will be calculated with 95% CI.
- GMC/GMT with 95% CI will be tabulated for antibodies against each antigen.

The above mentioned descriptive analyses will also be performed by race and sex.

The distribution of antibody concentrations/titers for each appropriate serotype/antigen will be displayed using tables and/or reverse cumulative distribution curves.

For anti-HBs antibodies, an analysis will be done according to vaccination history to Hepatitis B vaccine.

6.3.1.2. Between group assessment

For each treatment group, one month after Dose 3 of routine infant vaccines at Visit 4 (Month 5) time-point:

- Two-sided asymptotic standardized 95% CIs for the difference in the percentage of subjects with titer/concentration above or equal to pre-specified clinical thresholds will be computed (HRV Liq group minus HRV Lyo group).
- The two-sided 95% CIs for the group GMC/GMT ratio (HRV Liq group over HRV Lyo group) will be computed using an ANOVA model on the logarithm10 transformation of the concentrations. The ANOVA model will include the vaccine group as fixed effects. In addition, for anti-HBs, the model will include the Hepatitis B vaccination history as co-variable.
- For the group comparison in anti-PT, FHA, PRN seroresponse at one month post dose 3, P-value for testing H0: P≤ 85% vs. H1: P>85% (P= % of subjects in HRV liq group with seroresponse (above a threshold that leads to 95% seroresponse in the HRV lyo group) will be computed. P-value will be computed by integrating on the p-value for the null hypothesis that the seroresponse rate in the HRV lyo group is <85% and the a-posteriori probability of the threshold in the HRV liq group.

6.3.1.3. Statistical methods

- The exact 95% CIs for a proportion within a group will be based on the method by Clopper [see section 11.1].
- The standardized asymptotic CI for the group difference in proportion is the method 6 described in the Newcombe paper [see section 11.1]
- The 95% CIs of the group GMC/GMT ratios will be computed using an ANOVA model on the logarithm10 transformation of the concentrations/titers. The ANOVA model will include the vaccine group as fixed effects. In addition, for anti-HBs, the model will include the Hepatitis B vaccination history as co-variable.
- The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown

variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer/concentration.

- P-value for seroresponse endpoint will be computed by integrating on the p-value for the null hypothesis that the seroresponse rate in the HRV lyo group is <85% and the a-posteriori probability of the threshold in the HRV liq group.

6.3.2. Additional considerations

Summaries will be generated by frequent race and by gender using PPS. 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:

The percentage of doses and of subjects reporting at least one symptom (solicited or unsolicited) during the 8 day (Day 1-Day 8) 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, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of doses and of subjects reporting each individual solicited general symptom will be computed, over the 8 day (Day 1-Day 8) 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, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit. For fever, additional analyses will be performed by 0.5°C increments. These calculations will also be performed by sex and race.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31 day (Day 1-Day 31) 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, for unsolicited AEs rated as grade 3 with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of subjects who started taking at least one concomitant medication, antipyretic medication and prophylactic antipyretic medication during the 8 day (Days 1-8) and 31 day (Days 1-31) follow-up period post-vaccination will be tabulated by dose, overall per subject and over all the doses.

Subjects who experienced at least one SAE during the entire study period (from Dose 1 till ESFU Contact at Month 10) will be reported and the SAEs will be described in detail.

6.4.2. Additional considerations

Safety analysis will be done per administered dose. 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.

AE relationship to vaccination is defined as the relationship to at least one study vaccine as identified by the investigator. In case the related vaccine has not been specified the adverse event will be considered related to all study vaccines. The percentage of subjects reporting of causally related solicited symptoms and unsolicited adverse events within the 31-day (Days 1-31) post-vaccination period will be provided by group for each study vaccine separately.

The planned analysis of the percentage of doses and of subjects reporting at least one grade 3 causally related symptom (solicited or unsolicited) during the 8 day (Day 1-Day 8) solicited follow-up period post-vaccination will not be generated considering this analysis is of limited clinical relevance and is not part of the standard analyses planned in other PCV free Rota studies.

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.

7.1. Control on type I error

A 2.5% nominal type I error will be used for each co-primary evaluation. To control the type I error below 2.5%, a hierarchical procedure will be used for the multiple study objectives. That is, an objective will be reached if its associated criterion is met and the previous objectives were reached. The same order in which the study objectives are listed in Section 3.1 will be considered for hypothesis testing.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Safety data that is as clean as possible will be analyzed for IDMC review. Details of the review are described in an IDMC charter. The final analyses of all data will be conducted after conclusion of the ESFU contact and will include the final analyses of immunogenicity, reactogenicity and safety.

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	E1_01	SR	Yes	Yes	TFL TOC first version - All TFLs

8.2. Statistical considerations for interim analyses

Not applicable

9. CHANGES FROM PLANNED ANALYSES

The planned analysis of the percentage of doses and of subjects reporting at least one grade 3 causally related symptom (solicited or unsolicited) during the 8 day (Day 1-Day 8) solicited follow-up period post-vaccination will not be generated considering this analysis is of limited clinical relevance and is not part of the standard analyses planned in other PCV free Rota studies.

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	PCV-free-HRV liquid vaccine co-administered with Pediarix, Hiberix and Prevenar 13
2	Lyo	HRV Lyophilised vaccine co-administered with Pediarix, Hiberix and Prevenar 13

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. Pertussis vaccine response analysis

Usually immunological titres above t*, a fixed cut-off, are used as surrogate of efficacy. Therefore, non-inferiority of a new vaccine is claimed when P(t*), the proportion of subjects with post-vaccination titres above t*, is not decreased as compared to a control vaccine by more than Δ, a pre-specified non-inferiority margin.

For pertussis non-inferiority on seroresponse,

let $P_i(t^*)$ be the percentage of subjects with titer above t* in group i, i=1 for Liquid and i=0 for lyo), the null hypothesis can be written as,

$$H_0: P_1(t^*) < 85\% = 95\% - \Delta$$

with t* calibrated so that $P_0(t^*) = 95\%$

Would t* be fixed, the p-value would be computed from a binomial distribution with probability=85%, N=number of subjects in group Liquid and n=the number subjects with titer above *t**.

As t* is random, the expected p-value can be computed accounting for the distribution of t* as $\int \Pr\{ \text{Bin}(n_1 , \tau - \Delta) > n_1 \, P_1(t^*)\} \, f_0(t^*) \, dt^*$

with $f_0(t^*)$ denoting the distribution of t^*.

Based on the hypothesis testing principle that the type I error is the expected percentage of falsely rejecting H0 when H0 is true, the proposed test is to reject H0 when the expected p-value is below the type I error.

The distribution of $f_0(t^*)$ will be estimated using a non-parametric bootstrapping (1000 repetitions) approach.

The operating characteristics of the method was assessed via simulations. The log-transformed antibody titre of a subject in study group i was obtained from a normally distributed random function with mean and variance (μ_i ,σ^2_i) (i=0 for the control group).

To simulate data under the condition that $P_1(t^*) = \tau - \Delta_A$,the values of μ_0 , σ_0, μ_1, and σ_1 were constraint so that $\mu_0 + \sigma_0 \; Z_\tau = \mu_1 + \sigma_1 \; Z_{\tau - \Delta A}$ with Zτ denoting the Probit function.

Simulations were done under 2 conditions:

- The null hypothesis that $P_1(t^*) = \tau - \Delta$: This allowed estimating the true type I error rate of tests supposed to control the type I error below 2.5%. This was estimated by the proportion of simulations for which the p-value rejected H_0: $P_1(t^*) < \tau - \Delta$ at significance level 2.5%
- The alternative hypothesis that $P_1(t^*) = \tau - \Delta_A$: This allowed estimating the power of the tests. This was estimated by the proportion of simulations for which the p-value rejected H_0: $P_1(t^*) < \tau - \Delta$ at significance level 2.5%

The simulation also included power and type I estimation when using Miettinen non-inferiority p-value with 10% margin. The simulation indicated that the proposed stat method controlled well the type I error.

Table 6 Power for a non-inferiority margin Δ =10%, $P_0(t^*)$=95% and a 2.5% significance level

μ_0	$\sigma_0=\sigma_1$	n_0	μ_1	n_1	$P_1(t^*)$	$Pval_s$	$Pval_n$
Impact of n_0							
0	1	100	0	300	95%	94.2%	77.9%
0	1	150	0	300	95%	96.3%	89.7%
0	1	300	0	300	95%	99.4%	98.1%
Impact of σ_0							
0	1	300	0	300	95%	99.4%	98.1%
0	10	300	0	300	95%	99.5%	98.6%
0	100	300	0	300	95%	99.4%	98.5%
Impact of true difference							
0	1	300	-.2	300	92.575%	90.9%	75.8%
0	1	300	-.3	300	91.066%	71.5%	45.1%
0	1	300	-.4	300	89.341%	47.8%	21.7%
Impact of n_1							
0	1	300	-.3	250	91.066%	68.8%	45.2%
0	1	300	-.3	200	91.066%	61.5%	40.8%
0	1	300	-.3	150	91.066%	53.4%	33.2%

Pvals = Power for the traditional method (Miettinen, 1985). The method assumes that t* is fixed
$Pval_n$ = Power for the proposed method

Table 7 Type I error for a non-inferiority margin Δ =10%, $P_0(t_v)$=95% and a 2.5% significance level

μ0	σ0	n0	μ1	σ1	n1	P1(t*)	Pvals	Pvaln
0	1	300	-0.6084	1	300	85%	7.9%	0.8%
0	1	300	0	1.5870	300	85%	3.2%	0.9%
0	1	300	-0.2	1.3941	300	85%	3.1%	0.9%

$Pval_s$ = type I error for the traditional (method Miettinen, 1985). The method assumes that *t** is fixed.
$Pval_n$ = type I error for the new method

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: in case day is missing, 15 is used. In case day & month are missing, 30June 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.
- Duration: Duration of an event is expressed in days. It is the number of days between the start & the stop dates + 1. Therefore duration is 1 day for an event starting & ending on the same day.

11.2.2. 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 (eg 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (eg dose 3).
- 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.

11.2.3. 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 (ie 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.

11.2.4. 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.

  Note that in the case of HBsAg the values between the assay cut-off of 6.2 mIU/mL (=lower level of detection) and 7.65 mIU/mL (=lower level of quantification) will be assigned the arbitrary value of 6.2 for the GMC computation. The assay cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3 of the protocol, except for rotavirus IgA, whose lower level of quantification is defined to be 13 U/mL.

- For all assays but rotavirus IgA, 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. For the rotavirus IgA seropositivity is defined as having a concentration above 20 U/mL.

- In general, the assay cut-off is the value under which there is no quantifiable result available. For an assay with a specific 'assay cut_off', numerical immuno result is derived from a character field (rawres):

  – If rawres is 'NEG' or '-' or '(-)', numeric result= assay cut_off/2,
  – if rawres is 'POS' or '+' or '(+)', numeric result = assay cut_off,
  – if rawres is '< value' and value<=assay cut_off, numeric result =assay cut_off/2,
  – if rawres is '< value' and value>assay cut_off, numeric result =value,
  – if rawres is '> value' and value<assay cut_off, numeric result =assay cut_off/2,
  – if rawres is '> value' and value>=assay cut_off, numeric result =value,
  – if rawres is '<= value' or '>= value' and value<assay cut_off, numeric result =assay cut_off/2,
  – if rawres is '<= value' or '>= value' and value>=assay cut_off, numeric result =value,
  – if rawres is a value < assay cut_off, numeric result = assay cut_off/2,
  – if rawres is a value >= assay cut_off, numeric result = rawres,
  – else numeric result is left blank.

11.2.5. Safety

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).

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.

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"administered 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 (at the lowest intensity).
- Intensity of the following solicited AEs will be assessed as described in Table 8 and Table 9.

Table 8 Intensity scales to be used by the parent(s)/LAR(s) for solicited symptoms during the solicited follow-up period

Adverse Event	Intensity grade	Parameter
Fever*		Record temperature in °C/°F using any age-appropriate route.
Irritability/Fussiness	0	Behavior as usual
	1	Crying more than usual/no effect on normal activity
	2	Crying more than usual/interferes with normal activity
	3	Crying that cannot be comforted/prevents normal activity
Diarrhea$		Record the number of looser than normal stools/day
Vomiting§		Record the number of vomiting episodes/day
Loss of appetite	0	Appetite as usual
	1	Eating less than usual/no effect on normal activity
	2	Eating less than usual/interferes with normal activity
	3	Not eating at all
Cough/runny nose	0	Normal
	1	Cough/runny nose which is easily tolerated
	2	Cough/runny nose which interferes with daily activity
	3	Cough/runny nose which prevents daily activity

*Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity, the axilla and the rectum.

$ Diarrhea is defined as passage of three or more looser than normal stools within a day.

§ Vomiting is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥1 hour after feeding within a day.

Table 9 Intensity scales for diarrhea, vomiting and fever occurring during the solicited period

Adverse Event	Intensity grade	Parameter
Diarrhea $	0	Normal (0-2 looser than normal stools/day)
	1	3 looser than normal stools/day
	2	4-5 looser than normal stools/day
	3	≥ 6 looser than normal stools/day
Vomiting §	0	Normal (no emesis)
	1	1 episode of vomiting/day
	2	2 episodes of vomiting/day
	3	≥ 3 episodes of vomiting/day
Fever	0	temperature < 38.0°C/100.4° F
	1	temperature ≥ 38.0°C/100.4° F – ≤ 38.5°C/101.3 F
	2	temperature > 38.5°C/101.3 F – ≤ 39.5°C/103.1 F
	3	temperature > 39.5°C/103.1 F

$ Diarrhea is defined as passage of three or more looser than normal stools within a day.

§ Vomiting is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥1 hour after feeding within a day.

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: 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

11.2.6. 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).

11.2.7. Number of decimals displayed

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
All summaries	% of difference, including LL & UL of CI	2
Demographic characteristics	Mean, median age, SD (age)	1
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
Immunogenicity	Ratio of GMT/GMC	2
Immunogenicity	GMT/GMC except Strepto	1
Immunogenicity	GMT/GMC for Strepto	2
Seroresponse	P-value	4

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.

Template 1 Number of subjects enrolled by center - Exposed Set

Center	HRV LIQ	HRV LYO	Total	
	n	n	n	%
PPD		37	151	12.6
PPD		20	80	6.7
PPD		29	118	9.8
PPD		20	78	6.5
All				

<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 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at Visit 3 - Exposed Set

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

HRV LIQ = HRV vaccine liquid formulation
HRV LYO = HRV vaccine HRV 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 3 Number of subjects at each visit and list of withdrawn subjects (Exposed Set)

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

Template 4 Number of subjects enrolled into the study as well as the number of subjects excluded from PPS analyses with reasons for exclusion

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

HRV LIQ = HRV vaccine liquid formulation Lot C HRV LYO = HRV vaccine HRV 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 5 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**
HRV LIQ	**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
HRV 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

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = HRV vaccine liquid formulation Lot C
HRV LYO = HRV vaccine HRV 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 6 Summary of demographic characteristics (Per Protocol Analysis Set of Immunogenicity)

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

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = HRV vaccine liquid formulation Lot C
HRV LYO = HRV vaccine HRV 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 Summary of no co-administered vaccination by dose - Exposed Set

Dose1	HRV LIQ N = 300		HRV LYO N = 300		Total N = 1200	
Characteristics	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Any	299	99.7	300	100	1199	99.9
Infanrix hexa	299	99.7	300	100	1199	99.9
Dose 2	**HRV LIQ N = 300**		**HRV LYO N = 299**		**Total N = 1197**	
Characteristics	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Any	298	99.3	299	100	1195	99.8
Infanrix hexa	298	99.3	299	100	1195	99.8

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = HRV vaccine liquid formulation Lot C
HRV LYO = HRV vaccine HRV 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 8 Summary of vaccinations other than Study vaccines administered from birth until Visit 3, excluding vaccination given on the day of HRV doses - Exposed Set

Before Dose 1	HRV LYO N = 300			Total N = 1200		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**
Any	25	25	8.3	67	67	5.6
BCG	25	25	8.3	66	66	5.5
Infanrix hexa™	0	0	0.0	1	1	0.1
Between Dose 1 and Dose 2§	**HRV LYO N = 300**			**Total N = 1200**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**
Any	0	0	0.0	2	1	0.1
Infanrix hexa™	0	0	0.0	2	1	0.1
Between Dose 2 and Visit 3*	**HRV LYO N = 299**			**Total N = 1197**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**
Any	290	290	97.0	1163	1162	97.1
DTPa+IPV+Hib	0	0	0.0	1	1	0.1
Infanrix hexa™	290	290	97.0	1162	1161	97.0

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = HRV vaccine liquid formulation Lot C
HRV LYO = HRV vaccine HRV 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 9 Study population (Exposed Set)

	<Each group> N=XXXX	Total N=XXXX
Number of subjects		
Planned, N	xxx	xxx
Randomised, N <cohort name>	xxx	xxx
Completed, n (%)	xxx (xx.x)	xxx (xx.x)
<Unknown>	xxx	xxx
Demographics		
N <cohort name>	xxx	xxx
Females:Males	xxx:xxx	xxx:xxx
Mean Age, <unit> (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median Age, <unit> (minimum, maximum)	xxx (xxx,xxx)	xxx (xxx,xxx)
<MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)
<SECOND MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)
<THIRD MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)

Short group label = long group label

Template 10 Difference in seropositivity/seroprotection rates for Anti- *(Each antigen)* antibody one month after dose 3 of routine childhood vaccination (Visit 6) between HRV Coadministration group and HRV separate administration group - ATP cohort for immunogenicity

						Difference in seropositivity (seroprotection) rate			
						Anti- *(Each antigen) (cut-off: unit)*			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
HRV_COA			HRV_SEP			HRV_COA minus HRV_SEP			

Notes:
N = number of subjects with available results
% = percentage of subjects who are seropositive (seroprotected) one month after Dose 3 of childhood routine vaccination (Visit 6)
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

Template 11 Ratio of anti-rotavirus IgA antibody GMCs at one month after Dose 2 of the HRV vaccine between each pair of the three lots of the HRV vaccine liquid formulation – Per Protocol Analysis Set of Immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
HRV LIQ	242	384.4	HRV LIQ	260	418.8	HRV LIQ /HRV LIQ	0.92	0.67*	1.26*

HRV LIQ = HRV vaccine liquid formulation Lot A HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = 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 12 P-value for the test on the difference in percentage of subjects with primary seroresponse to Pertussis antigens between groups (Hiberix and ActHIB) one month after booster vaccination (Booster ATP Cohort for immunogenicity)

	Cutoff	Treatment Group Hiberix			Control Group ActHIB			P-value
Antibody	**Value**	**N**	**n**	**%**	**N**	**n**	**%**	**H0:P(t)≤ 85%**
Anti-FHA	144	791	705	89.1%	275	248	90.2%	<.0001
Anti-PRN	25	789	741	93.9%	275	250	90.9%	<.0001
Anti-PT	34	792	706	89.1%	275	248	90.2%	<.0001

Hiberix = Pooled Hiberix Lot A, Lot B and Lot C co-administered with Pediatrix, Prevnar 13 and Rotarix
ActHIB = ActHIB co-administered with Pediatrix, Prevnar 13 and Rotarix
Pentacel = Pentacel co-administered with Prevnar 13, Engerix-B and Rotarix
N = number of subjects with available results
n/% = number/percentage of results above the cutoff
Cutoff is the 95% percentile of the antibody level concentration in the control group
P-value is computed by integrating on the p-values of one-sided test with alpha=0.025 and the posterior probability of the cut-off in the control group

Template 13 Anti-rotavirus IgA antibody GMC and seropositivity rates – Per Protocol Analysis Set of Immunogenicity

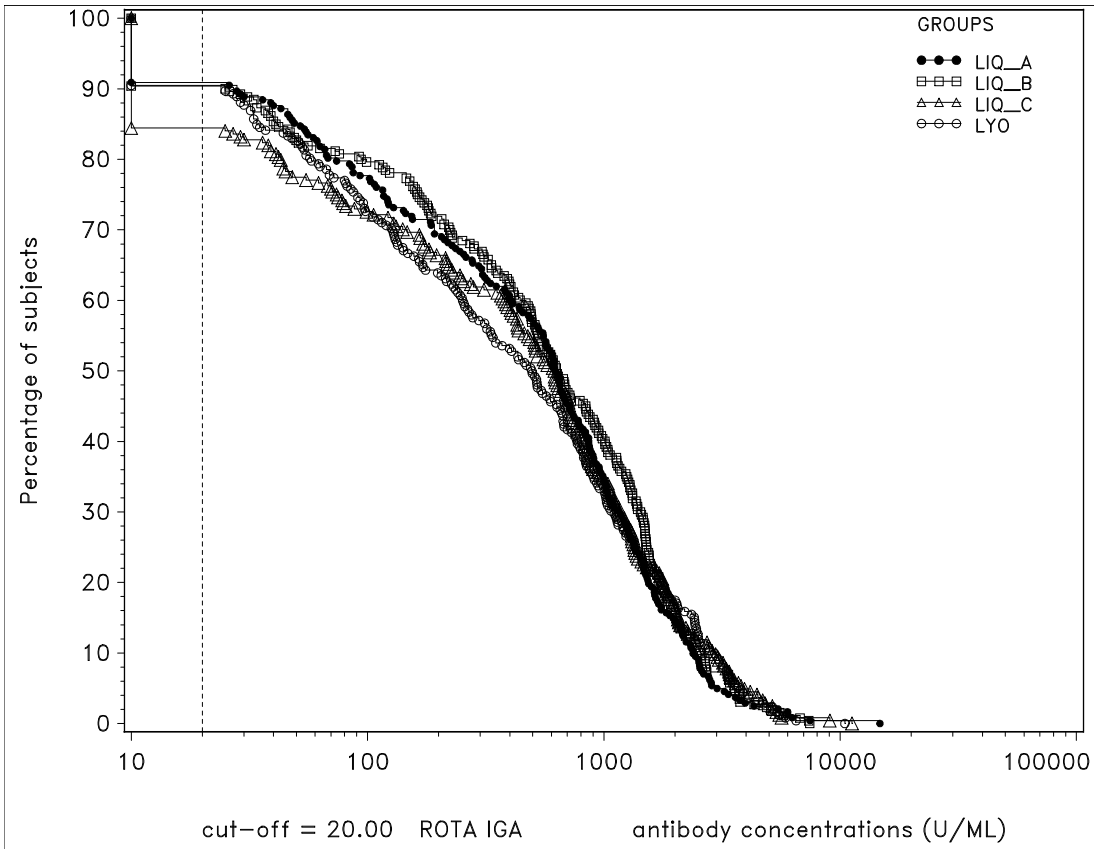
			≥ 20 U/ml				GMC (U/ml)		
					95% CI			95% CI	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
HRV LIQ	PRE	244	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	244	206	84.4	79.3	88.7	324.4	253.4	415.3
HRV LYO	PRE	252	0	0.0	0.0	1.5	<20	-	-
	PII(M2)	252	228	90.5	86.2	93.8	331.8	265.0	415.4

HRV LIQ = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
HRV LYO = HRV vaccine HRV 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 14 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 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

		HRV LIQ N = 300		HRV LYO N = 300		Total N = 1200	
VACCINE	Total number of doses received	n	%	n	%	n	%
Pediarix	1	0	0.0	1	0.3	3	0.3
	2	300	100	299	99.7	1197	99.8
	3						
Any	Any	300	100	300	100	1200	100
Hiberix	1	0	0.0	1	0.3	3	0.3
	2	300	100	299	99.7	1197	99.8
	3						
Any	Any	300	100	300	100	1200	100
Prevnar	1	0	0.0	1	0.3	3	0.3
	2	300	100	299	99.7	1197	99.8
	3						
Any ON COAD	Any	300	100	300	100	1200	100

HRV LIQ = HRV vaccine Liquid formulation lot A HRV LIQ = HRV vaccine Liquid formulation lot B
HRV LIQ = HRV vaccine Liquid formulation lot C HRV LYO = HRV vaccine HRV 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	HRV LIQ	298	10	298	100
	HRV LIQ	302	7	302	100
	HRV LIQ	300	6	300	100
	LIQPOOL	900	23	900	100
	HRV LYO	300	6	299	99.7
2	HRV LIQ	297	12	296	99.7
	HRV LIQ	301	6	301	100
	HRV LIQ	300	13	299	99.7
	LIQPOOL	898	31	896	99.8
	HRV LYO	299	9	297	99.3
Total	HRV LIQ	595	22	594	99.8
	HRV LIQ	603	13	603	100
	HRV LIQ	600	19	599	99.8
	LIQPOOL	1798	54	1796	99.9
	HRV LYO	599	15	596	99.5

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = HRV vaccine liquid formulation Lot C
LIQPOOL = Pooled HRV vaccine liquid formulation
HRV LYO = HRV vaccine HRV 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 1 to Day 8) follow-up period - Exposed Set

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

HRV LIQ = HRV vaccine liquid formulation Lot A HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = HRV vaccine liquid formulation Lot C LIQPOOL = Pooled HRV vaccine liquid formulation
HRV LYO = HRV vaccine HRV 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 doses with solicited general symptom including those rated grade 3 in intensity and those assessed as related to vaccination during the 8-day (Day 1 to Day 8) follow-up period, for each dose in the pooled HRV vaccine liquid formulation group and the HRV vaccine HRV Lyophilised formulation group - Exposed Set

		LIQPOOL					HRV 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
HRV LYO = HRV vaccine HRV 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 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 vaccine liquid formulation group and the HRV vaccine HRV Lyophilised formulation group - Exposed Set

		LIQPOOL					HRV LYO				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose											
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

LIQPOOL = Pooled HRV vaccine liquid formulation
HRV LYO = HRV vaccine HRV 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 subjects with grade 3 unsolicited symptoms classified by MedDRA SOC and PT from Day 0 to Day 30 after any vaccination in each HRV vaccine liquid formulation group - Exposed Set

Primary System Organ Class (CODE)	Preferred Term (CODE)	HRV LIQ N = 298				HRV LIQ N = 302				HRV LIQ 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)	HRV LIQ N = 298				HRV LIQ N = 302				HRV LIQ 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

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = 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 22 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA SOC and PT from Day 0 to Day 30 after vaccination in each HRV vaccine liquid formulation group - Exposed Set

		HRV LIQ N = 603				HRV LIQ N = 600			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		30	5.0	3.4	7.0	38	6.3	4.5	8.6
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	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
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	2	0.3	0.0	1.2	1	0.2	0.0	0.9
	Flatulence (10016766)	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	1	0.2	0.0	0.9
	Injection site pain (10022086)	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	1	0.2	0.0	0.9
	Irritability (10022998)	1	0.2	0.0	0.9	1	0.2	0.0	0.9
	Pyrexia (10037660)	3	0.5	0.1	1.4	4	0.7	0.2	1.7
Immune system disorders (10021428)	Hypersensitivity (10020751)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Infections and infestations (10021881)	Bronchitis (10006451)	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Ear infection (10014011)	3	0.5	0.1	1.4	2	0.3	0.0	1.2
	Exanthema subitum (10015586)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Eye infection (10015929)	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Gastroenteritis (10017888)	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Impetigo (10021531)	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Influenza (10022000)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Laryngitis (10023874)	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Otitis media (10033078)	7	1.2	0.5	2.4	12	2.0	1.0	3.5
	Perianal abscess (10034447)	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Pneumonia (10035664)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Respiratory tract infection (10062352)	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	1	0.2	0.0	0.9
	Rhinitis (10039083)	1	0.2	0.0	0.9	3	0.5	0.1	1.5
	Upper respiratory tract infection (10046306)	6	1.0	0.4	2.2	8	1.3	0.6	2.6
	Varicella (10046980)	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	1	0.2	0.0	0.9
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	1	0.2	0.0	0.9	6	1.0	0.4	2.2
	Nasal congestion (10028735)	0	0.0	0.0	0.6	0	0.0	0.0	0.6
	Rales (10037833)	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	0	0.0	0.0	0.6
	Eczema (10014184)	0	0.0	0.0	0.6	1	0.2	0.0	0.9

		HRV LIQ N = 603				HRV LIQ N = 600			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
	Rash (10037844)	0	0.0	0.0	0.6	0	0.0	0.0	0.6

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = 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 23 Number (%) of subjects with serious adverse events from first study vaccination up to Visit 3 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 24 Subjects with Serious Adverse Events reported up to Visit 3 - Exposed Set

Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
PPD	PPD	12	M	Kawasaki's disease	Kawasaki's disease	Infections and infestations	HO	1	12	29	N	Recovered/resolved
PPD	PPD	18	M	Influenza-b	Influenza	Infections and infestations	HO	2	2	5	N	Recovered/resolved
PPD	PPD	17	M	Acute gastroenteritis	Gastroenteritis	Infections and infestations	HO	2	9	5	N	Recovered/resolved
PPD	PPD	17	F	Infantile spasms	Infantile spasms	Nervous system disorders	HO	2	2	51	N	Recovered/resolved with sequelae
PPD	PPD	21	M	Rs-virus bronchiolitis	Respiratory syncytial virus bronchiolitis	Infections and infestations	HO	2	30	16	N	Recovered/resolved
PPD	PPD	13	M	Gastroenteritis	Gastroenteritis	Infections and infestations	HO	1	25	6	N	Recovered/resolved
PPD	PPD	22	M	Pneumonia	Pneumonia	Infections and infestations	HO	2	32	13	N	Recovered/resolved
		23		Middle ear infection	Otitis media	Infections and infestations	HO	2	37	8	N	Recovered/resolved
PPD	PPD	14	F	Secretory otitis media	Otitis media	Infections and infestations	HO	1	7	25	N	Recovered/resolved
PPD	PPD	20	M	Viral pneumonia	Pneumonia viral	Infections and infestations	HO	2	13	23	N	Recovered/resolved
	PPD	14	M	Middle ear infection, left	Otitis media	Infections and infestations	HO	1	19	8	N	Recovered/resolved
		14		Pneumonia	Pneumonia	Infections and infestations	HO	1	19	8	N	Recovered/resolved
PPD	PPD	13	M	Acute lymphadenitis	Lymphadenitis	Blood and lymphatic system disorders	HO	1	13	22	N	Recovered/resolved
PPD	PPD	10	F	Pyelonephritis acute	Pyelonephritis acute	Infections and infestations	HO	1	6	12	N	Recovered/resolved
PPD	PPD	19	M	Laryngitis	Laryngitis	Infections and infestations	HO	2	11	7	N	Recovered/resolved
PPD	PPD	14	M	Bronchitis acuta	Bronchitis	Infections and infestations	HO	1	23	12	N	Recovered/resolved
PPD	PPD	19	M	Bronchiolitis acuta	Bronchiolitis	Infections and infestations	HO	2	26	7	N	Recovered/resolved
PPD	PPD	19	F	Laryngitis acuta	Laryngitis	Infections and infestations	HO	2	7	4	N	Recovered/resolved
PPD	PPD	18	F	Laryngitis	Laryngitis	Infections and infestations	HO	2	7	4	N	Recovered/resolved
PPD	PPD	14	F	Gastroenteritis	Gastroenteritis	Infections and infestations	HO	1	22	7	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 25 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 vaccine liquid formulation group - Exposed Set

	HRV LIQ					HRV LIQ					HRV LIQ				
				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

HRV LIQ = HRV vaccine liquid formulation Lot A
HRV LIQ = HRV vaccine liquid formulation Lot B
HRV LIQ = 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 26 Solicited and Unsolicited symptoms experienced by at least 5 % of subjects classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period - AE below 5 % and SAE excluded (Total vaccinated cohort)

		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 27 Percentage of subjects with at least one episode of regurgitation Exposed Set

		Regurgitation									
		Group 1					Group 2				
					95% CI					95% CI	
		N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1	No	298	251	84.2	79.6	88.2	251		84.2	79.6	88.2
	Yes: with replacement	302	267	88.4	84.3	91.8	267	298	88.4	84.3	91.8
	Yes: without replacement	300	247	82.3	77.5	86.5	247	302	82.3	77.5	86.5
Dose 2	No	298	251	84.2	79.6	88.2	251	300	84.2	79.6	88.2
	Yes: with replacement	302	267	88.4	84.3	91.8	267	298	88.4	84.3	91.8
	Yes: without replacement	300	247	82.3	77.5	86.5	247	302	82.3	77.5	86.5
Overall/subject	No	298	251	84.2	79.6	88.2	251	300	84.2	79.6	88.2
	Yes: with replacement	302	267	88.4	84.3	91.8	267	298	88.4	84.3	91.8
	Yes: without replacement	300	247	82.3	77.5	86.5	247	302	82.3	77.5	86.5

N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one regurgitation episode 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:

Template 28 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 29 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 30 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 31 Percentage of subjects reporting of systemic solicited symptoms and unsolicited adverse events within the 31-day (Days 0-30) post-vaccination period which were assessed as causally related to each study vaccine separately (Primary Total Vaccinated Cohort)

		Vaccine A					Vaccine B					Vaccine C				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose	Hiberix	8053	6664	82.8	81.9	83.6	8052	6163	76.5	75.6	77.5	8049	4354	54.1	53.0	55.2
	ActHIB	1443	1213	84.1	82.1	85.9	1442	1115	77.3	75.1	79.5	1442	875	60.7	58.1	63.2
	Pentacel	1404	1174	83.6	81.6	85.5	1404	1065	75.9	73.5	78.1	1404	876	62.4	59.8	64.9
Overall/subject	Hiberix	2848	2688	94.4	93.5	95.2	2848	2601	91.3	90.2	92.3	2846	2116	74.3	72.7	75.9
	ActHIB	503	479	95.2	93.0	96.9	503	455	90.5	87.5	92.9	503	404	80.3	76.6	83.7

Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
Pentacel = *Pentacel* co-administered with *Prevnar13*, *Engerix-B* and *Rotarix*
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit