GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 3, 4.5 and 6 months of age and a booster dose at 18 months of age in healthy infants in Russia.
eTrack study number and Abbreviated Title	116194 [DTPA-IPV (INFANRIX-IPV)-061]
Scope:	All analyses as planned per protocol and for study report.
Date of Statistical Analysis Plan	First version: 16-Feb-2015 Amendment 1: 10-Aug-2017 Amendment 2: 14-Dec-2017
Co-ordinating author:	PPD (Lead Statistician) and PPD (Statistician)
Reviewed by:	PPD (Clinical and Epidemiology R&D Project Leader) PPD, Clinical Research and Development Lead (CRDL) PPD (peer reviewer statistician) PPD (public disclosure) PPD (Lead statistical analyst) PPD (Scientific writer) PPD (Global Regulatory Affairs) PPD (Safety Physician)
Approved by:	PPD (Clinical and Epidemiology R&D Project Leader) PPD, Clinical Research and Development Lead (CRDL) 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
ATP	Per Protocol Set
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	TVC
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
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

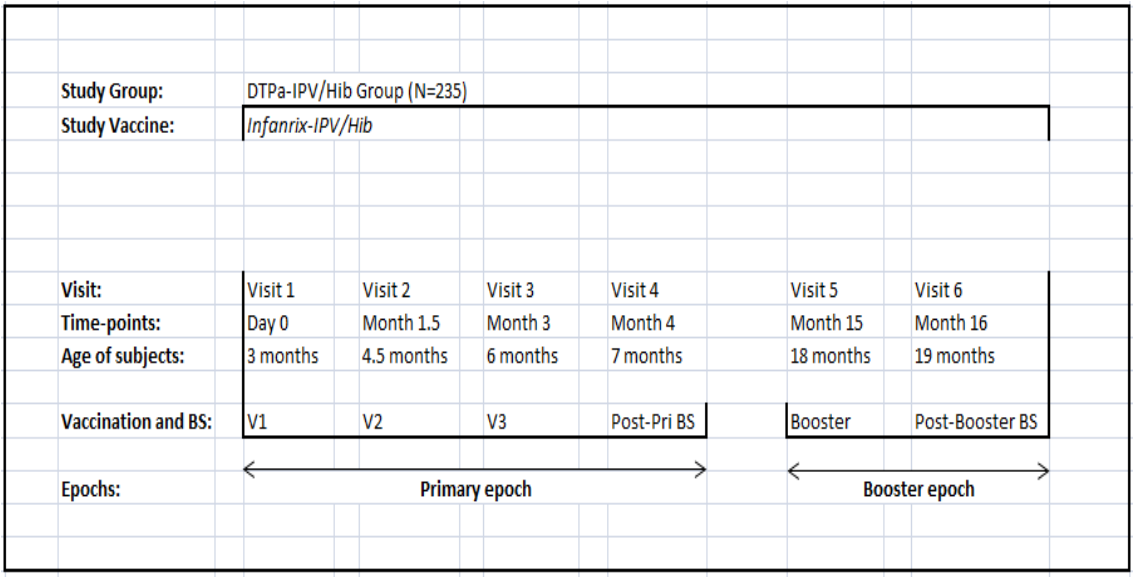
Date	Description	Protocol Version
16-FEB-2015	first version	Protocol 24-March-2014
10-AUG-2017	Amendment 1	Protocol Amendment 1 dated 11 October 2016
14-DEC-2017	Amendment 2	Protocol Amendment 1 dated 11 October 2016

The SAP amendment 1 was prepared in order to

1. Account for the new assay cut-off: During the course of the study, the assays used to measure the anti-D, -T, -PT, -FHA and -PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISAs for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISAs in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA's have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/ml for anti-D, 0.043 IU/ml for anti-T, 2.693 IU/ml for anti-PT, 2.046 IU/ml for anti-FHA and 2.187 IU/ml for anti-PRN. An agreement between the old and new ELISAs was shown with regards to the two thresholds of clinical relevance for the DI/TE response (0.1 IU/mL and 1.0 IU/mL) and therefore the clinical endpoints and anti-D and anti-T are unchanged. In the absence of a correlate of protection for the pertussis antigens, the anti- PT, anti-FHA and anti-PRN antibody seropositivity endpoints were redefined based on the new assay cut-off.
2. Use the SAP template effective since 14-April-2017
3. Reflect the protocol amendment 1

The SAP amendment 2 was prepared in order to include the interim analysis of the primary vaccination epoch in the sequence of analysis and in order to reflect the way important protocol deviation will be summarised (Important protocol deviation not leading to elimination will be described using narrative instead of summary table).

2. STUDY DESIGN



V = Primary vaccination
BS = Blood Sample
Post-Pri = One month after the third dose of primary vaccination course
Post-Booster = One month after booster vaccination

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 from the protocol), are essential and required for study conduct.

- Experimental design: Phase III, open-label, multi-centric, single-country study with a single group.
- Duration of the study: The intended duration of the study is approximately 16 months, per subject.
  - Epoch 001 (Primary epoch): Primary phase starting at Visit 1 (Day 0) and ending at Visit 4 (Month 4).
  - Epoch 002 (Booster epoch): Booster phase starting at Visit 5 (Month 15) and ending at Visit 6 (Month 16).

Study group: The study group and epochs foreseen in the study are presented in Table 1.

Table 1 Study group and epochs foreseen in the study

Study group	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001 (Primary epoch)	Epoch 002 (Booster epoch)
DTPa-IPV/Hib Group	~ 235	3 months - 4 months	x	
DTPa-IPV/Hib Group	~ 235	18 months – 19 months		x

The study group and treatment foreseen in the study are presented in Table 2.

Table 2 Study group and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Group
		DTPa-IPV/Hib Group
Infanrix-IPV/Hib	DTPa-IPV	x
	Hib	x

- Control: uncontrolled.
- Treatment group and vaccination schedule: All subjects will receive three doses of primary vaccination at 3, 4.5 and 6 months of age and a single dose of booster vaccination at 18 months of age.
  - DTPa-IPV/Hib Group: Subjects who will receive DTPa-IPV/Hib vaccine (*Infanrix-IPV/Hib*).
- Blinding: This is an open-label study (Refer to Table 3).

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001 (Primary epoch)	open
Epoch 002 (Booster epoch)	open

- Sampling schedule: Two blood samples (approximately 3.5 ml each) will be taken from all subjects: one blood sample will be taken one month after the primary vaccination course (Visit 4) and the second blood sample will be taken one month after the booster vaccination (Visit 6).
- Type of study: This is a self-contained study.
- Data collection: electronic Case Report Form (eCRF).

3. OBJECTIVES

3.1. Primary objectives

- To assess the immune response to the study vaccine in terms of seroprotection status for diphtheria, tetanus, Hib and poliovirus types 1, 2 and 3 antigens, and in terms of seropositivity to the pertussis antigens, one month after the third dose of primary vaccination.

Refer to Section 4.1 for the definition of the primary endpoint.

3.2. Secondary objectives

- To assess the immune response to the study vaccine in terms of seroprotection to diphtheria, tetanus, Hib and poliovirus types 1, 2 and 3 antigens, and in terms of seropositivity to the pertussis antigens, one month after the booster vaccination.
- To assess the immune response to the study vaccine in terms of antibody concentrations or titres against diphtheria, tetanus, Hib, poliovirus types 1, 2 and 3 antigens, and pertussis antigens, one month after the third dose of primary vaccination and one month after the booster vaccination.
- To assess the safety and reactogenicity of the study vaccine in terms of solicited symptoms, unsolicited symptoms and serious adverse events (SAEs).

Refer to Section 4.2 for the definition of the secondary endpoints.

4. ENDPOINTS

4.1. Primary endpoints

Immunogenicity with respect to components of the study vaccine.

- Anti-diphtheria, anti-tetanus, anti poliovirus types 1, 2 and 3, and anti-PRP seroprotection status, one month after the third dose of primary vaccination.
- Anti- PT, anti-FHA and anti-PRN antibody seropositivity status, one month after the third dose of primary vaccination.

4.2. Secondary

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria, anti-tetanus, anti poliovirus types 1, 2 and 3, and anti-PRP seroprotection status, one month after the booster vaccination.
  - Anti- PT, anti-FHA and anti-PRN antibody seropositivity status, one month after the Booster vaccination.
  - Anti-diphtheria, anti-tetanus, anti-poliovirus types 1, 2 and 3, anti-PRP, anti-PT, anti-FHA, anti-PRN antibody concentrations or titres, one month after the third dose of primary vaccination and one month after the booster vaccination.
- Solicited local and general symptoms.
  - Occurrence of solicited local/general symptoms during the 4-day (Days 0-3) follow-up period after each primary vaccination dose and following the booster vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited symptoms during the 31-day (Days 0-30) follow-up period after each primary vaccination dose and following the booster vaccination.
- Serious adverse events.
  - Occurrence of SAEs from Dose 1 up to study end.

5. ANALYSIS SETS

5.1. Definition

5.1.1. Total vaccinated cohort (TVC)

The Total vaccinated cohort for the primary epoch will include all subjects who received at least one primary vaccine dose. Thus, the Total vaccinated cohort for analysis of safety of the primary epoch will include all subjects with at least one primary vaccine dose administration documented and the Total vaccinated cohort for analysis of immunogenicity will include vaccinated subjects for whom data concerning primary immunogenicity endpoint measures are available.

The Total vaccinated cohort for the booster epoch will include all subjects who received the booster vaccine dose. Thus, the Total vaccinated cohort for analysis of immunogenicity for the booster epoch will include vaccinated subjects for whom data concerning booster immunogenicity endpoint measures are available.

5.1.2. According-to-protocol cohort for analysis of immunogenicity of the primary epoch

The ATP cohort for analysis of immunogenicity of the primary epoch will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals relative to the primary epoch defined in the protocol, with no elimination criteria during the primary epoch of the study) for whom data concerning primary immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component one month after Dose 3. The interval between Dose 3 and blood sampling at Visit 4, considered for inclusion of a subject will be 21-48 days.

5.1.3. Total vaccinated cohort for the booster epoch

The Total vaccinated cohort for the booster epoch will include all subjects who received the booster dose of study vaccine.

- The TVC for the analysis of safety of booster epoch will include all subjects with booster vaccine dose administration documented.
- The Total vaccinated cohort for analysis of immunogenicity of the booster epoch will include vaccinated subjects for whom data concerning booster immunogenicity endpoint measures are available.

5.1.4. According-to-protocol cohort for analysis of immunogenicity of the booster epoch

- The ATP cohort for analysis of immunogenicity of the booster epoch will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals relative to the booster epoch defined in the protocol, with no elimination criteria during the primary and booster epoches of the study) for whom data concerning immunogenicity endpoint measures of booster epoch are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component one month after the booster dose of vaccination. The interval between study visits that will be considered for inclusion in the ATP cohort for immunogenicity of booster epoch will be 15–18 months from date of birth to booster vaccination visit and 21-48 days between the booster vaccination visit and the blood sampling at one month post-booster vaccination.

5.1.5. Adapted ATP cohort

Adapted ATP cohort for analysis of immunogenicity will be used for tables presenting immunogenicity data from both the primary and booster epoch to indicate that the ATP cohort for analysis of immunogenicity of the primary epoch is used for endpoint at visit 4 (one month post primary) and that the ATP cohort for analysis of immunogenicity of the booster epoch is used for endpoints at visit 6 (one month post booster).

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 Total vaccinated cohort (TVC)

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 TVC. The epoch indicator (PR for primary, BO for booster) will be used to indicate the epoch for which data was eliminated.

5.2.2. Elimination from ATP cohort for immunogenicity

5.2.2.1. Excluded subjects

A subject will be excluded from the ATP cohort for immunogenicity under the following conditions

Code	Decode => Condition under which the code is used
900	Questionable subject => Invalid informed consent or fraudulent data. In case informed consent is obtained retrospectively the subject is not eliminated.
1030	Study vaccine dose not administrated at all but subject number allocated => subjects enrolled but not vaccinated
2010	Protocol violation (inclusion/exclusion criteria) => ineligible subject: age outside of (90-120 days) at the time of the first vaccination Other considerations as stated in section 4.2 – 4.3 in the protocol
2120	Obvious incoherence or abnormality or error in data => BS result available while BS not taken Post booster results below post-primary results for all available assays tested

5.2.2.2. Right censored Data

Code	Decode => Condition under which the code is used
1040	Administration of vaccine(s) forbidden in the protocol => Use of an investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period. A vaccine not foreseen by the study protocol administered during the period starting from 30 days before each dose of vaccine and ending 30 days after*, with the exception of hepatitis B vaccine and other vaccines given as part of the national immunisation schedule, that are allowed at any time during the study period. Seasonal or pandemic influenza vaccine can be given at any time during the study, and according to the Summary of Product Characteristics and national recommendations. *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
1070	Study vaccine dose not administered according to protocol => Route of vaccination is not Intramuscular for DTPa-PV/Hib Incomplete vaccination course of DTPa-PV/Hib regardless of dropout. Wrong reconstitution of the DTPa-PV/Hib before injection
1080	Vaccine temperature deviation => DTPa-PV/Hib vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090	Expired vaccine administered=> Subjects who received an expired DTPa-PV/Hib vaccine
2040	Administration of any medication forbidden by the protocol:=> Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab). Use of immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period. 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..
2070	Concomitant infection not related to the vaccine which may influence immune response = > Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (i.e. pertussis infection) or are confirmed to have an alteration of their initial immune status.
2080	Non-compliance with vaccination schedule => Subjects who did not comply with the vaccination interval of 28-62 days between doses age outside of (540-570 days) at the time of the booster vaccination

5.2.2.3. Visit-specific censored Data

Code	Decode => Condition under which the code is used
2090	Non-compliance with the blood sampling schedule (including wrong and unknown dates) => Blood sample not collected within 21 days-48 days after the booster dose of the DTPa-PV/Hib vaccine (Visit 6). Blood sample not collected within 21 days-48 days after the third dose of the DTPa-PV/Hib vaccine (Visit 4).
2100	Essential serological data missing => No serological results at all available post-primary (Visit 4) No serological results at all available post-booster (Visit 6) or at

5.3. Important protocol deviation not leading to elimination from ATP cohort for immunogenicity

Refer to the protocol deviation management plan for important protocol deviation not leading to elimination from ATP cohort for immunogenicity.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Section 11 and will not be repeated below.

6.1. Demography

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

The analysis of demographics will be performed separately for each epoch:

- The distribution of subjects enrolled among the study centers will be tabulated.
- The number of subjects who withdraw from the study will be tabulated according to the reason for drop-out.
- The deviations from specifications for age and intervals between study visits will be tabulated.

The median, mean, range and standard deviation of age (in weeks) at each vaccine dose will be computed. The median, mean and standard deviation of height in centimeter (cm) and weight in kilograms (kg) at Visit 1 will be computed. The Body Mass Index (BMI) at Visit 1 will also be computed as weight (in kg) / height^2 (in meters). The gender composition and geographic ancestry will be presented.

6.1.2. Additional considerations

The distribution of subjects enrolled among centers and the summary of subjects withdrawal will be generatd for the full study on the total vaccinated cohort. All demography summaries will be generated for the TVC and the 2 ATP cohorts. This will include BMI, gender composition and geographic ancestry. Age at first primary vaccination and age at booster vaccination will be computed in weeks.

Number and reason for elimination from each ATP cohort will be tabulated.

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.

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

The analysis of immunogenicity will be performed separately for each epoch.

The primary analysis will be based on the ATP cohort for analysis of immunogenicity for both primary and booster epochs. If the percentage of enrolled subjects excluded from this ATP cohort is more than 5%, a second analysis based on the Total vaccinated cohort will be performed on both primary and booster epochs to complement the ATP analysis. All analyses are descriptive.

Where appropriate, at each time-point that a blood-sample result is available:

- Seroprotection rates against diphtheria toxoid, tetanus toxoid, PRP antigen and poliovirus types 1, 2 and 3 antigens (with exact 95% CI) will be calculated.
- Seropositivity rates against PT, FHA and PRN antigens (with exact 95%) will be calculated.
- GMCs/GMTs with 95% CI will be tabulated for antibodies against each antigen.

The distribution of antibody concentrations/titres for each antigen will be displayed using reverse cumulative distribution curves (RCCs).

Handling of missing data:

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, analyses will exclude subjects with missing or non-evaluable measurements.

6.3.2. Additional considerations

The immunogenicity summaries will be generated on the adapted ATP cohort for immunogenicity.

For anti-PRP, the percentage of subjects with antibody concentrations ≥ 1.0 μg/ml will also be presented with exact 95% CI.

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

Analysis of safety relative to the primary epoch will include analysis of safety data collected following administration of the three primary doses of study vaccine. Analysis of safety relative to the booster epoch will include analysis of safety data collected following administration of the booster dose of study vaccine. At this second stage, in order to avoid missing SAEs that have been reported, an SAE summary table including all the events reported during the entire study period will also be generated.

The analysis will be based on the Total vaccinated cohort for both primary and booster epochs. All analyses are descriptive.

- The overall percentage of subjects/doses with at least one local symptom (solicited or unsolicited), with at least one general symptom (solicited or unsolicited) and with any symptom (solicited or unsolicited) during the 4-day (Days 0-3) solicited follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall primary doses. The same calculations will be done for symptoms (solicited or unsolicited) rated as grade 3 in intensity, for symptoms (solicited or unsolicited) leading to medical advice and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.
- The overall percentage of subjects/doses and of subjects reporting each individual solicited local and general symptom during the 4-day (Days 0-3) solicited follow-up period will be tabulated after each vaccine dose and overall primary doses, with exact 95% CI after each vaccine dose and overall primary doses. The same calculations will be done for each individual solicited symptom rated as grade 3 in intensity and for each individual solicited symptom assessed as causally related to vaccination.
- Occurrence of fever will be reported per 0.5°C cumulative increments.

- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day (Days 0-30) follow-up period after any dose (after primary or booster vaccination) with its exact 95% CI will be tabulated by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and AE(s)/SAE(s) leading to withdrawal from the study.
- The percentage of subjects who receive at least one concomitant medication during the 4-day (Days 0-3) solicited follow-up period and during the entire primary/booster epoch will be tabulated (with exact 95% CI after each vaccine dose and overall.
- Any large injection site reaction **(**defined as a swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase in limb circumference) after booster vaccination will be described in detail.

SAE(s) will be described in detail.

Handling of missing data:

- For a given subject and the analysis of solicited symptoms four days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e., symptom screen completed).
- For analysis of unsolicited AEs, such as SAEs or AEs by primary Medical Dictionary for Regulatory Activities (MedDRA) term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects, who do not report the event or the concomitant medication, will be considered as subjects without the event or the concomitant medication, respectively.
- For summaries reporting both solicited symptoms and unsolicited AEs, all vaccinated subjects will be considered. Subjects, who do not report the event or the concomitant medication, will be considered as subjects without the event or the concomitant medication, respectively.

6.4.2. Additional considerations

The summary of each solicited symptom and unsolicited adverse event will also be done for medically attended symptom/adverse event and for grade 3 causally related.

The percentage of subjects who receive concomitant medication and antipyretic medication during the entire study period will be tabulated for the 31-day (Day 0-30) follow-up period since this is the period planned for collecting concomitant medications.

7. ANALYSIS INTERPRETATION

All analyses will be conducted in a descriptive manner.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The analyses will be performed stepwise:

- A final analysis of the primary epoch will be conducted on all immunogenicity and safety data obtained up to one month after administration of the third primary dose of study vaccine (Visit 4), as soon as the data will be as clean as possible. This will include the analysis of the primary immunogenicity objectives related to the primary epoch and analysis of solicited symptoms and unsolicited adverse events reported within the 4-day (Days 0-3) period and 31-day (Days 0-30) period following the primary vaccination, respectively, and the SAEs reported during the primary epoch.
- Analysis of the booster epoch will be conducted on all cleaned immunogenicity and safety data obtained up to one month after administration of the booster dose of study vaccine (Visit 6). This will include analysis of the secondary immunogenicity objectives related to the booster epoch and analysis of solicited symptoms and unsolicited adverse events reported within the 4-day (Days 0-3) period and 31-day (Days 0-30) period following administration of the booster dose of study vaccine, respectively, and the SAEs reported during the booster epoch. At this second stage, in order to avoid missing SAEs that have been reported, an SAE summary table including all the events reported during the entire study period will also be generated.

8.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

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
Primary Epoch Analysis	E1_01	CTRS	Yes	No	TFL TOC
Final Analysis	E1_02	SR and CTRS	Yes	Yes	TFL TOC

8.3. Statistical considerations for interim analyses

The study is descriptive and the interim analysis will be performed on final/clean data. Therefore there is no adjustment for multiplicity resulting from the interim analysis.

9. CHANGES FROM PLANNED ANALYSES

Reference to ATP cohort for safety was removed in the description of the ATP cohort for immunogenicity as the ATP cohort for safety was not defined

The Total vaccinated cohort for the booster epoch was defined section 5.1.1

Note that the 2 first secondary endpoints described in the protocol:synopsis refer erroneously to results one month after the Third dose of the primary vaccination as opposed to the secondary endpoints described in the body of the protocol which refer one month post-booster vaccination.

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 contain 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 Section 13 of this SAP.

The following group name 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	DTPa-IPV/Hib	DTPa-IPV/Hib at 3, 4.5, 6 and 18 months of age

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].

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 0 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.

11.2.2. 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 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 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

- A seronegative subject is a subject whose antibody concentration/titre is below the assay cut-off.
- A seropositive subject is a subject whose antibody concentration/titre is greater than or equal to the assay cut-off.
- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU/ml.
  - Anti-tetanus antibody concentrations ≥ 0.1 IU/ml.
  - Anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8.
  - Anti-PRP antibody concentrations ≥ 0.15 μg/ml.
- The geometric mean titres (GMTs)/geometric mean concentrations (GMCs) calculations will be performed by taking the anti-log of the mean of the log10 titre/concentration transformations. Antibody titres/concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation.
- 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

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 4 and below

Table 4 Intensity scales to be used by the parent(s)/LAR(s) for solicited symptoms during the solicited follow-up period

Infant		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

*Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0 : Absent
1 : ≤ 5 mm
2 : > 5 mm and ≤ 20 mm
3 : > 20 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

		Axillary/Tympanic/Oral
0	:	< 37.5°C / 99.5°F
1	:	≥ 37.5°C / 99.5°F and ≤ 38.0°C / 100.4°F
2	:	> 38.0°C / 100.4°F and ≤ 39.0°C / 102.2°F
3	:	> 39.0°C / 102.2°F

In case temperature is recorded rectally, a conversion to Axillary temperature will be performed by removing 0.5°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	All subjects with solicited symptoms documented as present or absent for at least one dose.	All doses with solicited symptoms documented as present or absent within 0-3 days post dose
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
Drowsiness	10013649	Drowsiness
Fever	10016558	Fever
Irritability/Fussiness	10022998	Irritability
Loss of appetite	10003028	Appetite lost
Pain	10022086	Injection site pain
Redness	10022098	Redness at injection site
Swelling	10053425	Swelling at injection site

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.1.1

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 recent studies. 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 – TVC

	Combo group	Control group	Total	
Center	**n**	**n**	**n**	**%**
PPD	20	21	41	9.1
PPD	27	28	55	12.2
PPD	7	7	14	3.1
PPD	16	16	32	7.1
PPD	27	26	53	11.8
PPD	26	26	52	11.5
PPD	25	25	50	11.1
PPD	23	24	47	10.4
PPD	22	22	44	9.8
PPD	24	25	49	10.9
PPD	7	7	14	3.1
All	224	227	451	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 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at Visit 3 - TVC

	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 (TVC)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
HRV Liq	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		
HRV 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 4 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP 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**		
TVC	**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
ATP	**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 (ATP) relative to the TVC (ES)

Template 5 Deviations from specifications for age and intervals between study visits - TVC

		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 (ATP cohort for 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/m²)	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 Study population (TVC)

Study population (Total vaccinated cohort)		
Number of subjects	**Combo group**	**Control group**
Planned, N	225	225
Randomised, N (Total Vaccinated Cohort)	224	227
Completed, n (%)	224 (100)	227 (100)
Demographics	**Combo group**	**Control group**
N (Total Vaccinated Cohort)	224	227
Females :Males	97:127	115:112
Mean Age, weeks (SD)	8.8 (1.1)	8.8 (1.1)
Median Age, weeks (minimum, maximum)	9 (7, 11)	9 (7, 11)
Most frequent race: Asian - East Asian Heritage, n (%)	224 (100)	226 (99.6)

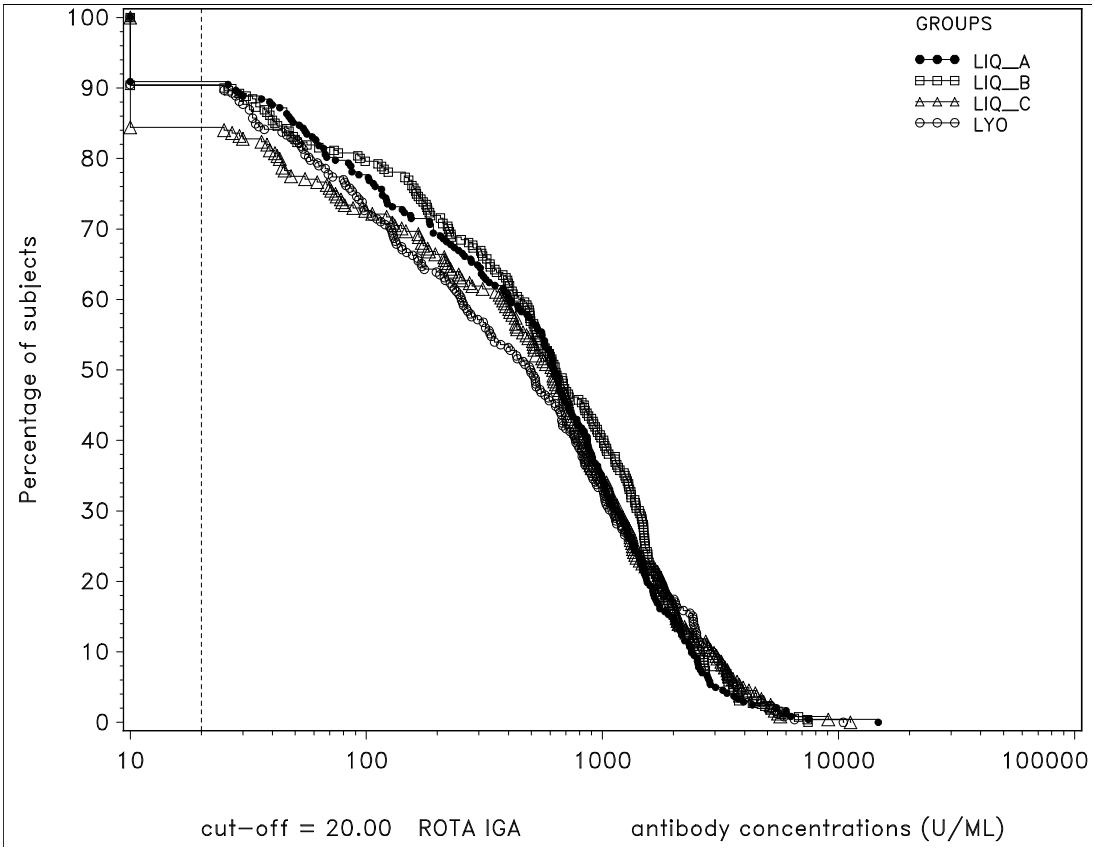
Combo group = Subjects received DTPa-IPV/Hib vaccine as a single injection at 2, 4 and 6 months of age
Control group = Subjects received DTPa-IPV and Hib vaccines at different injection sites at 2, 4 and 6 months of age
N = Total number of subjects enrolled in the study
n/% = Number/percentage of subjects in a given category
SD = Standard Deviation
MeaAge = Age calculated from Date of birth to first study vaccination

Template 8 Anti-rotavirus IgA antibody GMC and seropositivity rates – ATP cohort for 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 9 Reverse cumulative distribution curve for anti-rotavirus IgA antibody concentrations at Visit 3 - ATP cohort for Immunogenicity



Template 10 Number and percentage of subjects who received study vaccine doses - TVC

		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 11 Compliance in returning symptom sheets - TVC

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 12 Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) period after vaccination following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 2	Combo group	224	18	8.0	4.8	12.4	224	7	3.1	1.3	6.3	224	12	5.4	2.8	9.2
	Control group	227	15	6.6	3.7	10.7	227	6	2.6	1.0	5.7	227	11	4.8	2.4	8.5
Dose 4	Combo group	224	29	12.9	8.8	18.1	224	6	2.7	1.0	5.7	224	26	11.6	7.7	16.5
	Control group	227	29	12.8	8.7	17.8	227	9	4.0	1.8	7.4	227	22	9.7	6.2	14.3
Dose 6	Combo group	224	25	11.2	7.4	16.0	224	8	3.6	1.6	6.9	224	18	8.0	4.8	12.4
	Control group	227	19	8.4	5.1	12.8	227	2	0.9	0.1	3.1	227	18	7.9	4.8	12.2
Overall/dose	Combo group	672	72	10.7	8.5	13.3	672	21	3.1	1.9	4.7	672	56	8.3	6.4	10.7
	Control group	681	63	9.3	7.2	11.7	681	17	2.5	1.5	4.0	681	51	7.5	5.6	9.7
Overall/subject	Combo group	224	60	26.8	21.1	33.1	224	21	9.4	5.9	14.0	224	44	19.6	14.7	25.5
	Control group	227	47	20.7	15.6	26.6	227	14	6.2	3.4	10.1	227	39	17.2	12.5	22.7

Combo group = Subjects received DTPa-IPV/Hib vaccine as a single injection at 2, 4 and 6 months of age
Control group = Subjects received DTPa-IPV and Hib vaccines at different injection sites at 2, 4 and 6 months of age
For each dose and overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 2, 4 and 6 are the doses where subjects has received study vaccine - DTPa-IPV/Hib vaccine in Combo group and DTPa-IPV and Hib in Control group

Template 13 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) period after vaccination following each dose and overall (Total vaccinated cohort)

		Combo group					Control group				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 2											
Pain	All	224	108	48.2	41.5	55.0	227	113	49.8	43.1	56.5
	Grade 3	224	5	2.2	0.7	5.1	227	8	3.5	1.5	6.8
Redness (mm)	All	224	133	59.4	52.6	65.9	227	119	52.4	45.7	59.1
	>20	224	4	1.8	0.5	4.5	227	3	1.3	0.3	3.8
Swelling (mm)	All	224	65	29.0	23.2	35.4	227	64	28.2	22.4	34.5
	>20	224	5	2.2	0.7	5.1	227	2	0.9	0.1	3.1
Dose 4											
Pain	All	224	81	36.2	29.9	42.8	227	88	38.8	32.4	45.4
	Grade 3	224	3	1.3	0.3	3.9	227	3	1.3	0.3	3.8
Redness (mm)	All	224	131	58.5	51.7	65.0	227	124	54.6	47.9	61.2
	>20	224	20	8.9	5.5	13.5	227	18	7.9	4.8	12.2
Swelling (mm)	All	224	85	37.9	31.6	44.7	227	78	34.4	28.2	40.9
	>20	224	9	4.0	1.9	7.5	227	4	1.8	0.5	4.5
Dose 6											
Pain	All	224	87	38.8	32.4	45.6	227	78	34.4	28.2	40.9
	Grade 3	224	1	0.4	0.0	2.5	227	3	1.3	0.3	3.8
Redness (mm)	All	224	128	57.1	50.4	63.7	227	122	53.7	47.0	60.4
	>20	224	14	6.3	3.5	10.3	227	14	6.2	3.4	10.1
Swelling (mm)	All	224	96	42.9	36.3	49.6	227	88	38.8	32.4	45.4
	>20	224	6	2.7	1.0	5.7	227	7	3.1	1.2	6.3
Overall/dose											
Pain	All	672	276	41.1	37.3	44.9	681	279	41.0	37.2	44.8
	Grade 3	672	9	1.3	0.6	2.5	681	14	2.1	1.1	3.4
Redness (mm)	All	672	392	58.3	5	62.1	681	365	53.6	49.8	57.4
	>20	672	38	5.7	4.0	7.7	681	35	5.1	3.6	7.1
Swelling (mm)	All	672	246	36.6	33.0	40.4	681	230	33.8	30.2	37.5
	>20	672	20	3.0	1.8	4.6	681	13	1.9	1.0	3.2
Overall/subject											
Pain	All	224	143	63.8	57.2	70.1	227	146	64.3	57.7	70.5
	Grade 3	224	9	4.0	1.9	7.5	227	12	5.3	2.8	9.1
Redness (mm)	All	224	177	79.0	73.1	84.2	227	167	73.6	67.3	79.2
	>20	224	29	12.9	8.8	18.1	227	26	11.5	7.6	16.3
Swelling (mm)	All	224	130	58.0	51.3	64.6	227	121	53.3	46.6	59.9
	>20	224	15	6.7	3.8	10.8	227	11	4.8	2.4	8.5

Combo group = Subjects received DTPa-IPV/Hib vaccine as a single injection at 2, 4 and 6 months of age
Control group = Subjects received DTPa-IPV and Hib vaccines at different injection sites at 2, 4 and 6 months of age
For each dose and overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
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
Dose 2, 4 and 6 are the doses where subjects has received study vaccine - DTPa-IPV/Hib vaccine in Combo group and DTPa-IPV and Hib in Control group
Grade 3 pain refers to severe significant pain at rest. Prevents normal every day activities.

Template 14 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 - TVC

		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 15 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 - TVC

		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 16 Incidence of any large injection site reaction (defined as a swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase in limb circumference) with onset within 4 days (Day 0–3) after booster vaccination (Total Vaccinated Cohort at Year 9)

Type of Swelling	(Each group) N=				Total N=			
	n	%	95%CI		n	%	95% CI	
			LL	UL			LL	UL
Any								
Local Swelling								
Diffuse Swelling								
Involving at least one adjacent joint								

Boostrix group= Subjects who had received GSK Biologicals' Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6

Adacel group= Subjects who had received Sanofi Pasteurs' Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6

Control group= Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6

N = Number of subjects with documented dose

n/% = number/percentage of subjects reporting a specified symptom

95% CI = Exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 17 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 - TVC

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
	Pneumonia (10035664)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	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
	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 18 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 - TVC

		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	Dermatitis allergic (10012434)	1	0.2	0.0	0.9	0	0.0	0.0	0.6

		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**
(10040785)	Eczema (10014184)	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	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 19 Number (%) of subjects with serious adverse events from first study vaccination up to Visit 3 including number of events reported (TVC)

			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 20 Subjects with Serious Adverse Events reported up to Visit 3 - TVC

Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
PP	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	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	HO	1	23	12	N	Recovered/resolved

Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
						infestations						
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 21 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 - TVC

	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
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
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
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

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 22 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 23 Minimum and maximum activity dates (TVC)

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 24 Number of enrolled subjects by age category (TVC)

		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 25 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 26 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)