Statistical Analysis Plan

Detailed Title:	A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids™ when co-administered with GSK Biologicals' oral live attenuated HRV liquid vaccine Rotarix™ in healthy Japanese infants aged 6 - 12 weeks at the time of the first dose of HRV vaccination.
eTrack study number and Abbreviated Title	114720 (ROTA-079)
Scope:	All data pertaining to the above study.
SAP Version	Version 1
SAP date	12-SEP-2016
Co-ordinating author:	PPD
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 (Lead Scientific writer) PPD (Regulatory Affair) PPD (Clinical Safety representative) PPD (CTRs)
Approved by:	PPD (Clinical and Epidemiology Project Lead) delegating to PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead Scientific writer)

FORM-9000026972-01 Statistical Analysis Plan Template (Effective date: pilot for process, target to be effective in January 2017)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

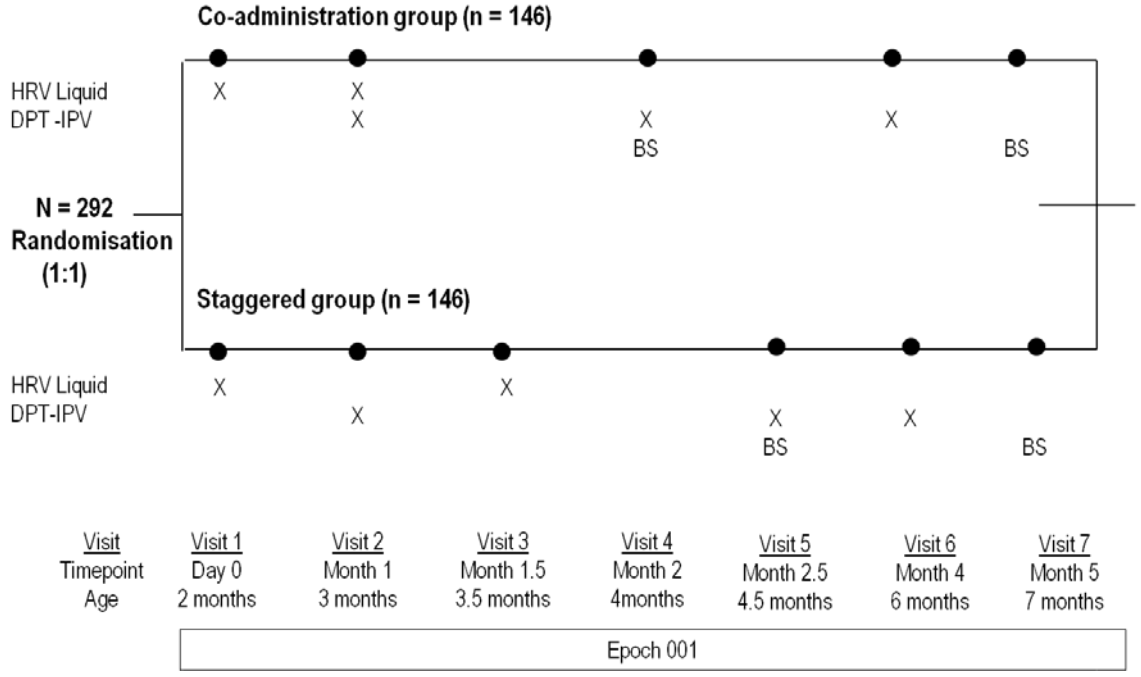
LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-To-Protocol
CI	Confidence Interval
BMI	Body Mass Index
CTRS	Clinical Trial Registry Summary
DPT	Diphtheria, Pertussis and Tetanus toxoids
eCRF	Electronic Case Report Form
ED50	Effective dose to inhibit 50% of the maximum
Eli Type	Internal GSK database code for type of elimination code
FHA	Filamentous Haemagglutinin
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
HRV	Human Rotavirus
IgA	Immunoglobulin A
IPV	Inactivated Poliovirus Vaccine
IU/ml	International unit per milliliter
LL	Lower Limit of the confidence interval
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
PT	Pertussis Toxoid
RV	Rotavirus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval
U/ml	Unit per milliliter

1. DOCUMENT HISTORY

Date	Description	Protocol Version
12-SEP-2016	Version 1: first version	Final – 03-JUN-2016

2. STUDY DESIGN



N = Number of subjects planned to be enrolled; n = Number of subjects in each group; BS = Blood Sampling.
Visit 3 and Visit 5 are applicable only for subjects in the Staggered group. Visit 4 is applicable only for subjects in the Co-administration group.

- Experimental design: Phase IV, open-label, randomised, controlled, multi-centric, single-country study with two parallel groups.
- Primary Completion Date: Visit 7 (Month 5)
- End of Study: Last testing results released of samples collected at Visit 7
- Study groups: The study groups and epoch foreseen in the study are provided in Table 1.

Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min/ - Max)	Epoch
			Epoch 001
Co-administration group	146	6 weeks - 12 weeks	x
Staggered group	146	6 weeks - 12 weeks	x

- The study groups and treatment foreseen in the study are provided in Table 2.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		Co-administration group	Staggered group
Rotarix	HRV	x	x
Squarekids	*Squarekids*	x	x

- Control: active control (Staggered group).
- Vaccination schedules: The vaccination schedules are as follows:
  - Subjects in the Co-administration group will be administered the DPT-IPV vaccine according to a 3, 4, 6 month schedule and the liquid HRV vaccine according to a 2, 3 month schedule.
  - Subjects in the Staggered group will be administered the DPT-IPV vaccine according to a 3, 4.5, 6 month schedule and the liquid HRV vaccine according to a 2, 3.5 month schedule.
- Treatment allocation: Randomised 1:1 using GSK Biologicals' central randomisation system on Internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for centre and stratified for a HRV immunogenicity sub-cohort.
- Blinding: Open-label.
- Sampling schedule: Details of the samples to be collected are as follows:
  - A blood sample of approximately 2 mL will be collected from a sub-cohort of subjects, 1 month after the administration of the second dose of the liquid HRV vaccine.
  - A blood sample of approximately 5 mL will be collected at Visit 7, 1 month after administration of the last dose of DPT-IPV vaccine from all the subjects.
- Details of the HRV Immunogenicity sub-cohort are provided in Table 3. The sub-cohort will consist of 146 subjects (the first 73 subjects enrolled into the study from each study group).

Table 3 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
HRV Immunogenicity sub-cohort	The serum anti-RV IgA antibody concentration and seropositivity 1 month after the second dose of the liquid HRV vaccine will be assessed in this sub-cohort of subjects.	146 subjects (approximately half the number of subjects (73) from each study group)*

* The first 73 subjects enrolled into each study group will be allocated to the sub-cohort.

- Recording of solicited local symptoms within 8 days follow-up period (Day 0 - Day 7) after the first dose of DPT-IPV vaccine.

- Recording of solicited general symptoms within 8 days follow-up period (Day 0 - Day 7) following administration of each dose of HRV vaccine and after the first dose of DPT-IPV vaccine.
- Recording of unsolicited symptoms within 31 days (Day 0- Day 30) following administration of each dose of HRV vaccine and after the first dose of DPT-IPV vaccine.
- Recording of causally related AEs from the first study vaccine up to Visit 7.
- Recording of SAEs from first study vaccine up to Visit 7.
- Recording of AEs/SAEs leading to withdrawal from the study from the first study vaccine.
- Recording of SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine from the time the subject consents to participate in the study until Visit 7.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

3. OBJECTIVES

3.1. Primary objective

- To demonstrate that the immunogenicity to the antigens contained in DPT-IPV vaccine is not impaired by the co-administration with GSK Biologicals' liquid HRV vaccine.

Criteria for non-inferiority (1 month after the third dose of DPT-IPV vaccine at Visit 7):

- Lower limits of the standardised asymptotic 95% confidence intervals (CIs) on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective concentrations ≥ 0.1 IU/mL for anti-diphtheria (anti-D) antibodies and concentrations ≥ 0.1 IU/mL for anti-tetanus (anti-T) antibodies are ≥-10% (clinical limit for non-inferiority),
- Lower limits of the 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with concentrations ≥ 10 IU/mL for antibodies against the pertussis toxoid (PT) and filamentous hemagglutinin (FHA) antigens (anti-PT and anti-FHA) are ≥ -10% (clinical limit for non-inferiority),
- Lower limits of the standardised asymptotic 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective titres (≥8 ED_{50}) for each of anti-poliovirus serotypes 1, 2 and 3 antibodies are ≥ -10% (clinical limit for non-inferiority).

3.2. Secondary objectives

- To assess the immunogenicity of the liquid HRV vaccine in terms of serum anti-RV IgA antibody seropositivity and Geometric Mean Concentrations (GMCs) in a sub-cohort of subjects, 1 month after the second dose of the liquid HRV vaccine.
- To assess the immunogenicity to all the antigens contained in the DPT-IPV vaccine in terms of GMCs/ geometric mean antibody titres (GMTs), 1 month after the third dose of the DPT-IPV vaccine.
- To assess reactogenicity and safety after each dose of liquid HRV vaccine and first dose of DPT-IPV vaccine in terms of solicited symptoms during the 8-day follow-up period and unsolicited symptoms during the 31-day follow-up period.
- To assess safety in terms of serious adverse events (SAEs) from the first dose of study vaccine up to study end.

4. ENDPOINTS

4.1. Primary endpoint

- Immunogenicity with respect to components of the DPT-IPV vaccine 1 month after administration of the third dose of the vaccine (Visit 7):
  - anti-diphtheria antibody concentrations $\geq$ 0.1 IU/mL,
  - anti-tetanus antibody concentrations $\geq$ 0.1 IU/mL,
  - anti-PT and anti-FHA antibody concentrations $\geq$ 10 IU/mL,
  - anti-poliovirus serotypes 1, 2 and 3 antibody titre $\geq$ 8 ED_{50}.

4.2. Secondary endpoints

- Serum anti-RV IgA antibody concentration and seropositivity in a sub-cohort of subjects, 1 month after the second dose of the liquid HRV vaccine.
- Serum GMCs/GMTs for anti-diphtheria, anti-tetanus, anti-poliovirus serotypes 1, 2 and 3, anti-PT and anti-FHA antibodies, 1 month after the third dose of the DPT-IPV vaccine.
- Occurrence of solicited general symptoms during the 8-day (Days 0-7) follow-up period after each dose of liquid HRV vaccine.
- Occurrence of solicited local and general symptoms during the 8-day (Days 0-7) follow-up period after the first dose of DPT-IPV vaccine.
- Occurrence of unsolicited AEs during the 31-day (Days 0-30) follow-up period after each dose of the liquid HRV vaccine and the first dose of DPT-IPV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs from the first dose of the study vaccine up to study end (Visit 7).

5. ANALYSIS SETS

5.1. Definition

Two cohorts are defined for the purpose of the analysis:

- Total vaccinated cohort.
- ATP cohort for analysis of immunogenicity.

5.1.1. Total vaccinated cohort

The TVC will include all subjects with at least one dose of the study vaccines administration documented:

- A safety and reactogenicity analysis based on the TVC will include all subjects with at least one vaccine administration documented.
- An immunogenicity analysis based on the TVC will include all subjects from this cohort for whom immunogenicity data were available.

The TVC analysis will be performed per treatment actually administered.

5.1.2. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for immunogenicity will include all eligible subjects:

- who comply with vaccination schedule of DPT-IPV and HRV vaccines,
- for whom the DPT-IPV and HRV vaccines were administered according to protocol
- who have not received vaccine/medication forbidden by the protocol (up to Visit 7),
- whose underlying medical condition was not forbidden by the protocol (up to Visit 7),
- who complied with the blood sampling schedule at visit 7,
- who had no concomitant infection related to any component of the DPT-IPV vaccine which may have influenced the immune response up to blood sample at visit 7,
- who had no concomitant infection unrelated to any component of the DPT-IPV vaccine which may have influenced the immune response up to blood sample at visit 7. Note that RV GE will not be considered as concomitant infection unrelated to any component of the DPT-IPV vaccine.
- for whom immunogenicity data are available for at least one antigen of the DPT-IPV vaccine at visit 7 sampling time point.

5.2. Criteria for eliminating data from Analysis Sets

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

5.2.1. Elimination from TVC

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

5.2.2. Elimination from ATP cohort for analysis of immunogenicity

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

Code Eli Type =MA	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine dose not administered at all but subject number allocated
1040	Administration of concomitant vaccine(s) forbidden in the protocol up to blood sample at visit 7
1050	Randomisation failure (subject not randomized in the correct group)
1070	Study vaccine dose not administered according to protocol: - Site or route of study vaccine administration wrong or unknown - Administration not according to protocol for reason specified by the investigator other than site and route - Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) - Only part of the multiple planned administrations at one visit has been administered
1080	Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by Status QA GMP NON Use
1090	Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration
2010	Protocol violation linked to the inclusion/exclusion criteria
2040	Administration of any medication forbidden by the protocol up to blood sample at visit 7
2050	Underlying medical condition forbidden by the protocol up to blood sample at visit 7
2060	Concomitant infection related to any component of the DPT-IPV vaccine which may influence the immune response up to blood sample at visit 7
2070	Concomitant infection not related to any component of the DPT-IPV vaccine other than RV GE which may influence the immune response up to blood sample at visit 7. Note that RV GE will not be considered as concomitant infection unrelated to any component of the DPT-IPV vaccine.
2080	Non compliance with vaccination schedule for HRV and/or DPT-IPV vaccination – see Table 4
2090	Non compliance with blood sample schedule at Visit 7 – see Table 4

Code Eli Type =MA	Condition under which the code is used
2100	Essential serological data missing: serological data missing for all antigens in the DPT-IPV vaccine at Visit 7
2120	Obvious incoherence, abnormal serology evolution or error in data (Eg; incoherence between CRF and results, wrong sample labelling)

Table 4 Intervals between study visits for code 2080 and *2090*

Study Group	Interval	Optimal length of interval [1]	Allowed interval[2]
Co-administration group	Visit 1→Visit 2*	30 days	28 days - 42 days
	Visit 2→Visit 4	30 days	28 days – 42days
	Visit 4→Visit 6	56 days	28 days - 56 days
	Visit 6→Visit 7	*30 days*	*21 days - 48 days*
Staggered group	Visit 1→Visit 2*	30 days	28 days - 42 days
	Visit 2→Visit 3	15 days	7 days - 21 days
	Visit 3→Visit 5**	30 days	28 days - 42 days
	Visit 5→Visit 6	45 days	28 days – 56 days
	Visit 6→Visit 7	*30 days*	*21 days - 48 days*

[1]. Whenever possible the investigator should arrange study visits within this interval.
[2]. Subjects will not be eligible for inclusion in the According To Protocol (ATP) cohort for analysis of immunogenicity if they make the study visit outside this interval.
* Visit 2 should take place when the subject is 3 months of age or older.
**The period between Visit 2 and Visit 5 should be within 8 weeks.
There should be a time-period of at least 7 days between the administration of an inactivated vaccine and any other vaccine, and 28 days between the administration of a live virus vaccine and any other vaccine, in Japan. Please refer to the package inserts of *Rotarix* and *Squarekids* for more details.

5.2.3. Right censored Data

Not applicable.

5.2.4. Visit-specific censored Data

Not applicable.

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

The following important protocol deviations will be reported by groups:

- Forced randomization: in case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

- Manual randomization: in case the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule.

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 distributions of subjects enrolled by centre will be tabulated by group.

The numbers of subjects who are withdrawn from the study will be tabulated by group according to the reason for withdrawal.

The median, mean, range and standard deviation (SD) of age at each study vaccine dose (in weeks) will be computed by group. The median, mean and SD of height in centimetre (cm) and weight in kilograms (kg) at Visit 1 will be computed by group. The Body Mass Index (BMI) at Visit 1 will also be computed as weight (in kg)/height^2 (in m). The gender composition per group will also be presented.

The deviations from specifications for age and intervals between study visits will be tabulated by group.

6.1.2. Additional considerations

The median, mean, range and standard deviation (SD) of gestational age (in weeks) will be computed by group.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The number of doses of the liquid HRV vaccine and DPT-IPV vaccine administered will be tabulated per group.

6.2.2. Additional considerations

None.

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

The ATP cohort for immunogenicity will be used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the TVC will be performed

only if more than 5% of the vaccinated subjects with immunogenicity results available were excluded from the ATP cohort for immunogenicity. In such a case, the TVC analyses will evaluate whether exclusion from the ATP cohort has biased the results.

Within group assessment

For each treatment group and each antigen:

- Percentage of subjects with antibody concentrations/ titres greater than or equal to the pre-specified cut-off will be calculated with exact 95% CI (Refer Table 9 of the protocol). Anti-PT and anti-FHA antibody concentrations ≥ 10 IU/mL will also be calculated with exact 95% CI.
- GMC/GMTs, as applicable with 95% CIs will be computed.
- The distribution of antibody concentrations/ titres, as applicable, will be presented using reverse cumulative curves (RCCs).

Between group assessment

For each antigen in the DPT-IPV vaccine:

- The two-sided asymptotic standardised 95% CIs for the difference between groups (Co-administration group minus Staggered group) in terms of percentage of subjects with antibody concentrations/ titres greater than or equal to the pre-specified cut-off will be computed. Anti-PT and anti-FHA antibody concentrations ≥ 10 IU/mL will also be calculated with exact 95% CI.

6.3.2. Additional considerations

The following seropositivity thresholds are applicable:

- anti-RV IgA antibody concentration ≥ 20 U/mL.
- anti- diphtheria antibody concentrations ≥ assay cut-off
- anti- tetanus antibody concentrations ≥ assay cut-off
- anti-PT antibody concentrations ≥ 2.693 IU/mL
- anti-FHA antibody concentrations ≥ 2.046 IU/mL

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.

Other cut-offs to be considered for summary tables and between-group comparisons

- Anti-PT antibody concentrations ≥ 10 IU/mL
- Anti-FHA antibody concentrations ≥ 10 IU/mL

Anti-rotavirus IgA antibody GMCs and their 95% CI will also be computed on subjects seropositive for anti-rotavirus IgA antibody.

A sensitivity analysis excluding forced randomization will be performed for the primary objectives in case the percentage of forced randomizations exceed 5% (forced randomizations are allocation which were constrained by supply available at the site. In open studies, allocations without using the randomization system are also forced randomizations).

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

The safety analysis will be based on the TVC.

The incidence by dose, overall per dose and overall per subject, with its exact 95% CI of

- any adverse event (solicited or unsolicited, local or general),
- at least one local adverse event (solicited or unsolicited), and,
- at least one general adverse event (solicited or unsolicited),

during the 8-day (Days 0-7) follow-up period will be tabulated. The same calculations will be performed for any Grade 3 (solicited or unsolicited) symptoms, related and for any adverse event requiring medical attention.

For each type of solicited symptom, the incidence during the 8-day (Days 0-7) follow-up period of the symptom (any grade, Grade 3, related, Grade 3 related, requiring medical advice) will be tabulated as follows:

- at each dose, the percentage of doses followed by the reporting of a symptom and its exact 95% CI,
- over all the doses, the percentage of subjects reporting the symptom and its exact 95% CI,
- over all the doses, the percentage of doses followed by the reporting of a symptom and its exact 95% CI,
- for fever, additional analyses will be performed by 0.5°C increments.

The percentage of subjects who receive concomitant medication, who receive antipyretic medication and prophylactic antipyretic medication during the 8-day (Days 0-7) and 31-day (Days 0-30) follow-up period post-vaccination will be tabulated by dose, overall per subject and over all the doses.

The verbatim reports of unsolicited symptoms 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 symptoms occurring during the 31 days (Days 0-30) with its exact 95% CI will be

tabulated by preferred term. Similar tabulation will be done for Grade 3 unsolicited symptoms and for unsolicited symptoms causally related to vaccination.

Subjects who experienced at least one SAE during the entire study period (from the first dose till the end of the study [Visit 7]) will be reported and the SAEs will be described in detail.

6.4.2. Additional considerations

- In line with the endpoint description separate analysis will be made for solicited symptom, unsolicited AE within 31 days post vaccination and concomitant medication for
  - The 2 HRV doses
  - The first DTPa-IPV dose
- In line with the HRV project standard, the primary analysis of solicited symptom will be performed by administered dose regardless of whether a solicited symptom has been documented as present/absent. A complementary analysis by documented dose in which only dose for which presence/absence of the symptoms is recorded will performed in case the percentage of documented dose among administered dose exceed 5% for one visit or a group.
- The incidence by dose, overall per dose and overall per subject of any grade 3 adverse event (solicited or unsolicited, local or general) with causal relationship to vaccination during the 8-day (Days 0-7) follow-up period will be tabulated with exact 95% CI.
- The percentage of subjects with unsolicited symptoms requiring medical attention occurring within 31 days (Days 0-30) post-vaccination with its exact 95% CI will be tabulated by group and preferred term. Similar tabulation will also be done for unsolicited AEs rated as grade 3 in intensity with causal relationship to vaccination.
- The percentage of subjects with causally related AEs from the first study vaccine until Visit 7 will be tabulated by group and preferred term.
- Medications will be coded using the GSKDRUG dictionary. Medications which started during the specified periods (Days 0-7 and Days 0-30) will be counted rather than all medications taken during the specified periods.
- For clintrial.gov and EudraCT posting purposes, a summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA as per the following codes:

Solicited symptom	Lower level code	Lower level term
Pain at injection site	10022086	Injection site pain
Redness at injection site	10022098	Injection site redness
Swelling at injection site	10053425	Injection site swelling
Fever	10016558	Fever
Irritability/Fussiness	10057224	Irritability postvaccinal

Solicited symptom	Lower level code	Lower level term
Diarrhoea	10012727	Diarrhea
Vomiting	10047700	Vomiting
Loss of appetite	10003028	Appetite lost
Cough/ runny nose	10011224	Cough
Drowsiness	10013649	Drowsiness

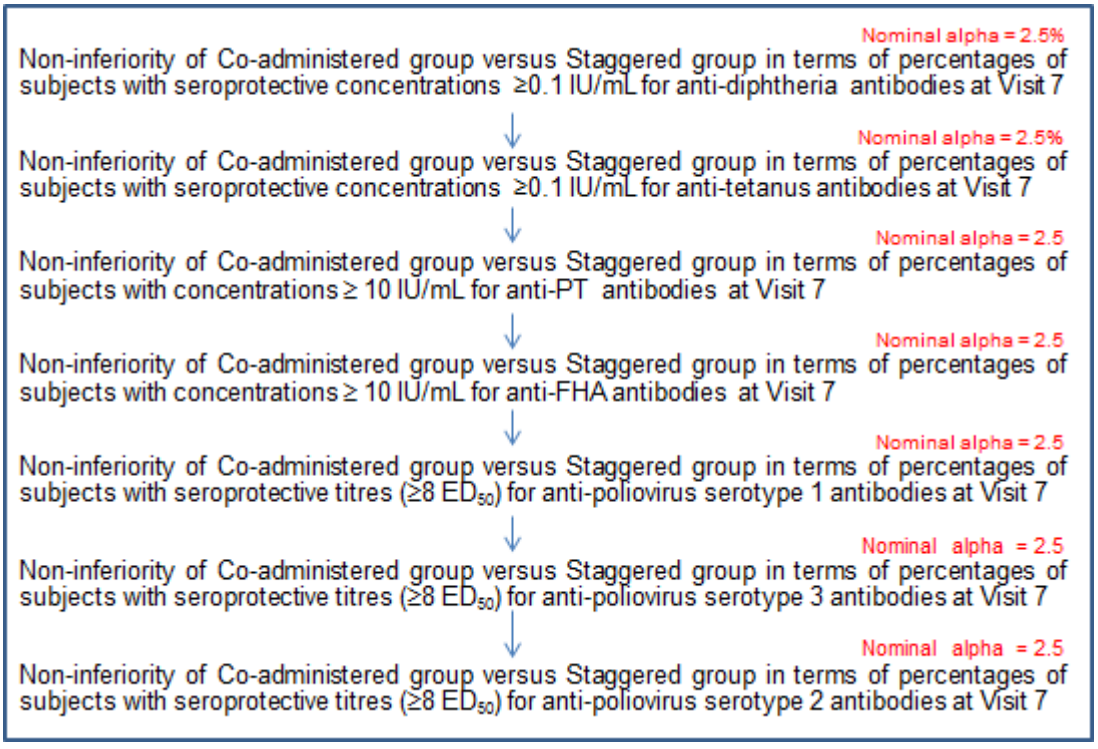
7. ANALYSIS INTERPRETATION

Except for analysis on objectives with predefined success criterion and an appropriate type I error control (i.e. confirmatory analyses), no comparative analyses will be performed.

With respect to confirmatory analyses the interpretation must be done in a hierarchical manner.

Each objective can only be reached if the associated criteria is met and all previous objectives have been reached (see Figure 1).

Figure 1 Sequence for evaluating the study objectives



The sequence of testing for anti-poliovirus antibodies was based on the fact that polio type 2 is eradicated and serotype 1 is the most prevalent followed by type 3 as per a 10:1 ratio (cases confirmed worldwide in the calendar year 2012 [data in World Health Organization (WHO) headquarter as of 12 March 2013]).

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

The final data analysis will include all data up to one month after the third dose of DPT-IPV vaccine. These analyses will include the final analysis of immunogenicity and the final analysis of solicited and unsolicited symptoms and SAEs from the first dose up to Visit 7.

Description	Analysis ID	Disclosure Purpose (CTRS=web posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)* requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	E1_01	Study Report CTRS	Y for in-text tables, to be generated between LSLV and 1 month before Data Base Freeze	Yes	All tables from TFL dated 12-SEP-2016

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.

9. CHANGES FROM PLANNED ANALYSES

It was planned in the protocol to exclude subjects without any available results for both sampling time points (Visits 4/5 and 7) from the ATP cohort for analysis of immunogenicity. Actually, subjects without any available results for the sampling time point at Visit 7 will be excluded from the ATP cohort for analysis of immunogenicity.

10. SPECIFICATIONS FOR 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,…).

The following group names will be used in the TFLs:

Group order in tables	Group label in tables	Group definition for footnote
1	Co-Administered	DPT-IPV vaccine administered according to a 3, 4, 6 month schedule and the liquid HRV vaccine according to a 2, 3 month schedule
2	Staggered	DPT-IPV vaccine administered according to a 3, 4.5, 6 month schedule and the liquid HRV vaccine according to a 2, 3.5 month schedule.

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.

11.2. 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 units between the date of birth and the reference activity.

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/Titres (GMC/Ts) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres 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 GMT calculation. The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3 of the protocol.
- A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay.
- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection.
- The assay cut-off is the value under which there is no quantifiable result available. For an assay with a specific 'cut_off' , numerical immuno result is derived from a character field (rawres):
  - If rawres is 'NEG' or '-' or '(-)', numeric result= cutt_off/2,
  - if rawres is 'POS' or '+' or '(+)', numeric result = cut_off,
  - if rawres is '< value' and value<=cut_off, numeric result =cut_off/2,
  - if rawres is '< value' and value>cut_off, numeric result =value,
  - if rawres is '> value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '> value' and value>=cut_off, numeric result =value,
  - if rawres is '<= value' or '>= value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '<= value' or '>= value' and value>=cut_off, numeric result =value,
  - if rawres is a value < cut_off, numeric result = cut_off/2,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - else numeric result is left blank.
- All CI computed will be two-sided 95% CI.

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.

- In case there will be more than 5% of subjects without documented dose for solicited symptoms (i.e., symptom screen not completed), sensitivity analysis will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed).
- The following rules will be used for the analysis of solicited symptoms:
  - Subject who didn't document the presence or absence of a solicited symptom after one dose will be considered not having that symptom after that dose in the analysis done on "administrated dose"
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
  - Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
  - Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be considered as having that symptom after that dose).
- The maximum intensity of local injection site redness/swelling will be coded as follows:

Grade	Redness/swelling
0	Absent
1	> 0 mm and ≤ 5 mm
2	> 5 mm and ≤ 20 mm
3	> 20 mm

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

Grade	Temperature
0	< 37.5°C
1	≥ 37.5°C - ≤ 38.0°C
2	> 38.0°C - ≤ 39.0°C
3	> 39.0°C

For rectal route, temperatures will be converted to axillary setting by subtracting 0.5°

- 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)
Solicited local symptom	Primary analysis: all subjects with study vaccine administered Sensitivity analysis: all subjects with at least one solicited local 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 local 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

- All CI computed will be two-sided 95% CI.

11.2.6. Data presentation description

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

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
Demographic characteristics	Mean, median, SD	1
Immunogenicity	% of difference, including LL & UL of CI	2
Immunogenicity	Anti-RV IgA GMC	1
Immunogenicity	Anti-diphtheria and anti-tetanus GMC	1
Immunogenicity	Anti-poliovirus serotypes 1, 2 and 3 GMT	1
Immunogenicity	Anti-PT and anti-FHA GMC	1

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to Section 5.2.

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following draft study specific mock 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-056, Study Report/DTPa-HBV-IPV-125 and additional web tables 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 by centre (Total vaccinated cohort)

	HRV	Placebo	Total	
Center	n	n	n	%
PPD	26	14	40	5.2
PPD	28	14	42	5.5
PPD	18	8	26	3.4
PPD	26	13	39	5.1
PPD	18	10	28	3.7
PPD	12	7	19	2.5
PPD	13	7	20	2.6
PPD	38	19	57	7.5
PPD	13	7	20	2.6
PPD	68	34	102	13.3
PPD	32	16	48	6.3
PPD	14	7	21	2.7
PPD	16	8	24	3.1
PPD	6	4	10	1.3
PPD	48	24	72	9.4
PPD	48	24	72	9.4
PPD	72	35	107	14.0
PPD	3	2	5	0.7
PPD	3	2	5	0.7
PPD	6	2	8	1.0
All	508	257	765	100

n = number of subjects included in each group or in total for a given centre or for all centres
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Centre = GSK Biologicals' assigned centre number

Template 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at Visit 4 – First year conclusion (Total vaccinated cohort)

	HRV	Placebo	Total
Number of subjects vaccinated	508	257	765
Number of subjects completed	492	247	739
Number of subjects withdrawn	16	10	26
Reasons for withdrawal :			
Serious Adverse Event	1	0	1
Non-serious adverse event	0	1	1
Protocol violation	0	1	1
Consent withdrawal (not due to an adverse event)	9	3	12
Migrated/moved from study area	6	2	8
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	3	3
Other - not reached			
Other - practical difficulty this year			

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed Visit 4
Withdrawn = number of subjects who did not come for Visit 4

Template 3 Number of subjects at each visit and list of withdrawn subjects up to visit 4 – First year conclusion (Total vaccinated cohort)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
HRV	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		
Placebo	VISIT 1	257		
			no. PP	PROTOCOL VIOLATION
			no. PP	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 in the sub-cohorts (Total vaccinated cohort)

		HRV N = 1666		Placebo N = 1667		Total N = 3333	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Sub-cohort	Immunogenicity sub cohort 1	306	18.4	306	18.4	612	18.4
	Immunogenicity sub cohort 2	153	9.2	153	9.2	306	9.2

N = number of subject number
n = number of subject number in a given category
% = n / Number of subject number with available results x 100

Template 5 Number of subjects enrolled into the study as well as the number excluded from ATP analyses (Reactogenicity/Safety and Immunogenicity) with reasons for exclusion

	Total			HRV		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	765						
Total vaccinated cohort	765		100	508		257	
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0
Essential serological data missing (code 2100)	3	3		3	3	0	0
Subject not planned to be bled for their all blood sampling visits (code 2130)	707	708		470	471	237	237
ATP cohort for immunogenicity	54		7.1	34		20	

Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Template 6 Summary of demographic characteristics (ATP cohort for Immunogenicity)

		HRV N = 34		Placebo N = 20		Total N = 54	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at Dose 1 of HRV	Mean	7.5	-	7.2	-	7.4	-
	SD	1.60	-	1.23	-	1.47	-
	Median	7.0	-	7.0	-	7.0	-
	Minimum	6	-	6	-	6	-
	Maximum	12	-	10	-	12	-
Age (weeks) at Dose 2 of HRV	Mean	12.7	-	12.0	-	12.4	-
	SD	1.57	-	1.45	-	1.55	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	11	-	10	-	10	-
	Maximum	11	-	10	-	10	-
	Missing	17	-	15	-	17	-
Age (weeks) at Dose 1 of DPT-IPV	Mean	12.7	-	12.0	-	12.4	-
	SD	1.57	-	1.45	-	1.55	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	11	-	10	-	10	-
	Maximum	11	-	10	-	10	-
	Missing	17	-	15	-	17	-
Age (weeks) at Dose 2 of DPT-IPV	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
	Missing						
Age (weeks) at Dose 3 of DPT-IPV	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
	Missing						
Gender	Female	14	41.2	14	70.0	28	51.9
	Male	20	58.8	6	30.0	26	48.1
Geographical ancestry	African heritage / African American	0	-	0	-	0	-
	American Indian or Alaskan native	0	-	0	-	0	-
	Asian - Central/South Asian heritage	0	-	0	-	0	-
	Asian - East Asian heritage	0	-	0	-	0	-
	Asian - Japanese heritage	34	100	20	100	54	100
	Asian - South east Asian heritage	0	-	0	-	0	-
	Native Hawaiian or other Pacific Islande	0	-	0	-	0	-
	White - Arabic / North African heritage	0	-	0	-	0	-
	White - Caucasian / European heritage	0	-	0	-	0	-
	Other	0	-	0	-	0	-

		HRV N = 34		Placebo N = 20		Total N = 54	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Height (cm) at visit 1	Mean	55.3	-	55.7	-	55.5	-
	SD	3.80	-	1.87	-	3.21	-
	Median	55.5	-	55.0	-	55.0	-
Weight (kg) at visit 1	Mean	5.2	-	5.1	-	5.1	-
	SD	0.66	-	0.49	-	0.60	-
	Median	5.1	-	5.2	-	5.2	-
BMI at visit 1 (kg/m²)	Mean						
	SD						
	Median						
Gestational age (weeks)	Mean						
	SD						
	Median						
	Minimum						
	Maximum						

N = total number of subjects in each group
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD= standard deviation
Database Lock Date = 31MAR2009

Template 7 Minimum and maximum activity dates (Total vaccinated cohort)

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 8 Deviations from specifications for age and intervals between study visits (Total vaccinated cohort)

		Age	PRE-Dose:1	Dose:1-Dose:2		Dose:2-PII(M2)	
Group		**Protocol**	**Protocol**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
		from 6 to 14 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	N	508	37	499	499	35	35
	n	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0
	range	6 to 14	0 to 0	30 to 47	30 to 47	30 to 45	30 to 45
Placebo	N	257	20	250	250	20	20
	n	1	0	0	0	0	0
	%	0.4	0.0	0.0	0.0	0.0	0.0
	range	5 to 14	0 to 0	30 to 47	30 to 47	30 to 42	30 to 42

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
PRE = pre-vaccination
PII(M2) = One month after the second dose (Visit 3)

Template 9 Study population (Total vaccinated cohort)

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

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

Template 10 Anti-rotavirus IgA antibody GMC and seropositivity rates - ATP cohort for immunogenicity

			≥ 20 U/mL				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV	PRE	34	0	0.0	0.0	10.3	<20	-	-
	PII(M2)	34	29	85.3	68.9	95.0	217.0	109.9	428.6
Placebo	PRE	20	0	0.0	0.0	16.8	<20	-	-
	PII(M2)	20	1	5.0	0.1	24.9	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration ≥ 20 U/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M2) = One month after the second dose (Visit 3)
PRE = pre-vaccination

Template 11 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies - ATP cohort for immunogenicity

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV	PII(M2)	29	368.9	202.1	673.3
Placebo	PII(M2)	1	496.0	-	-

GMC = geometric mean antibody concentration calculated on subjects with concentration ≥ 20 U/mL
N = number of subjects who seroconverted for Anti-rotavirus IgA Antibody
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M2) = One month after the second dose (Visit 3)

Template 12 Seroprotection rates and GMC for anti-Diphtheria and anti-Tetanus antibody concentrations by groups at pre booster vaccination (ATP cohort for analysis of antibody persistence)

				≥ 0.1 IU/ml				≥ 1 IU/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti- Diphtheria	Group A	Pre-BST	271	241	88.9	84.6	92.4	1	0.4	0.0	2.0	0.175	0.163	0.188
	Group B	Pre-BST	272	250	91.9	88.0	94.9	0	0.0	0.0	1.3	0.189	0.176	0.202
	Control	Pre-BST	279	234	83.9	79.0	88.0	2	0.7	0.1	2.6	0.154	0.142	0.166
Anti-Tetanus	Group A	Pre-BST	272	269	98.9	96.8	99.8	8	2.9	1.3	5.7	0.450	0.423	0.478
	Group B	Pre-BST	273	271	99.3	97.4	99.9	10	3.7	1.8	6.6	0.509	0.481	0.540
	Control	Pre-BST	278	275	98.9	96.9	99.8	6	2.2	0.8	4.6	0.380	0.359	0.404

Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age in the primary study
Group B = Subjects who received DTPa-IPV/Hib vaccine at 3, 4, 5 months of age in the primary study
Control = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age in the primary study
Seroprotection=Anti-Diphtheria and Anti-Tetanus antibody concentration ≥0.1 IU/ml
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-BST=Pre-booster vaccination blood sampling time point

Template 13 Seropositivity rates and GMC for anti-PT by groups at pre booster vaccination (ATP cohort for analysis of antibody persistence)

				≥ 2.693 IU/mL				≥ 10 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PT	Group A	Pre-BST	272	260	95.6	92.4	97.7	38	14.0	10.1	18.7	10.3	9.6	11.1
	Group B	Pre-BST	273	263	96.3	93.4	98.2	62	22.7	17.9	28.1	12.2	11.3	13.1
	Control	Pre-BST	280	260	92.9	89.2	95.6	43	15.4	11.3	20.1	10.4	9.6	11.2

Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age in the primary study
Group B = Subjects who received DTPa-IPV/Hib vaccine at 3, 4, 5 months of age in the primary study
Control = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age in the primary study
Seropositivity =Anti-PT antibody concentration ≥ 5 ELU/ml
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-BST=Pre-booster vaccination blood sampling time point

Template 14 Seroprotection rates and geometric mean titres (GMT) for anti-Poliovirus 1, 2 and 3 antibody by groups at pre vaccination (ATP cohort for analysis of antibody persistence)

				≥ 8 ED_{50}				GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-Poliovirus 1	Group A	Pre-BST	272	259	95.2	92.0	97.4	72.3	62.4	83.7
	Group B	Pre-BST	273	267	97.8	95.3	99.2	95.7	82.5	111.0
	Control	Pre-BST	280	270	96.4	93.5	98.3	77.2	67.0	89.0
Anti-Poliovirus 2	Group A	Pre-BST	272	248	91.2	87.2	94.3	57.3	47.0	70.0
	Group B	Pre-BST	273	261	95.6	92.4	97.7	63.6	53.5	75.5
	Control	Pre-BST	280	250	89.3	85.1	92.7	42.6	35.7	50.8
Anti-Poliovirus 3	Group A	Pre-BST	272	254	93.4	89.7	96.0	71.3	60.1	84.7
	Group B	Pre-BST	273	259	94.9	91.5	97.2	79.9	66.4	96.2
	Control	Pre-BST	280	257	91.8	87.9	94.7	60.6	51.2	71.8

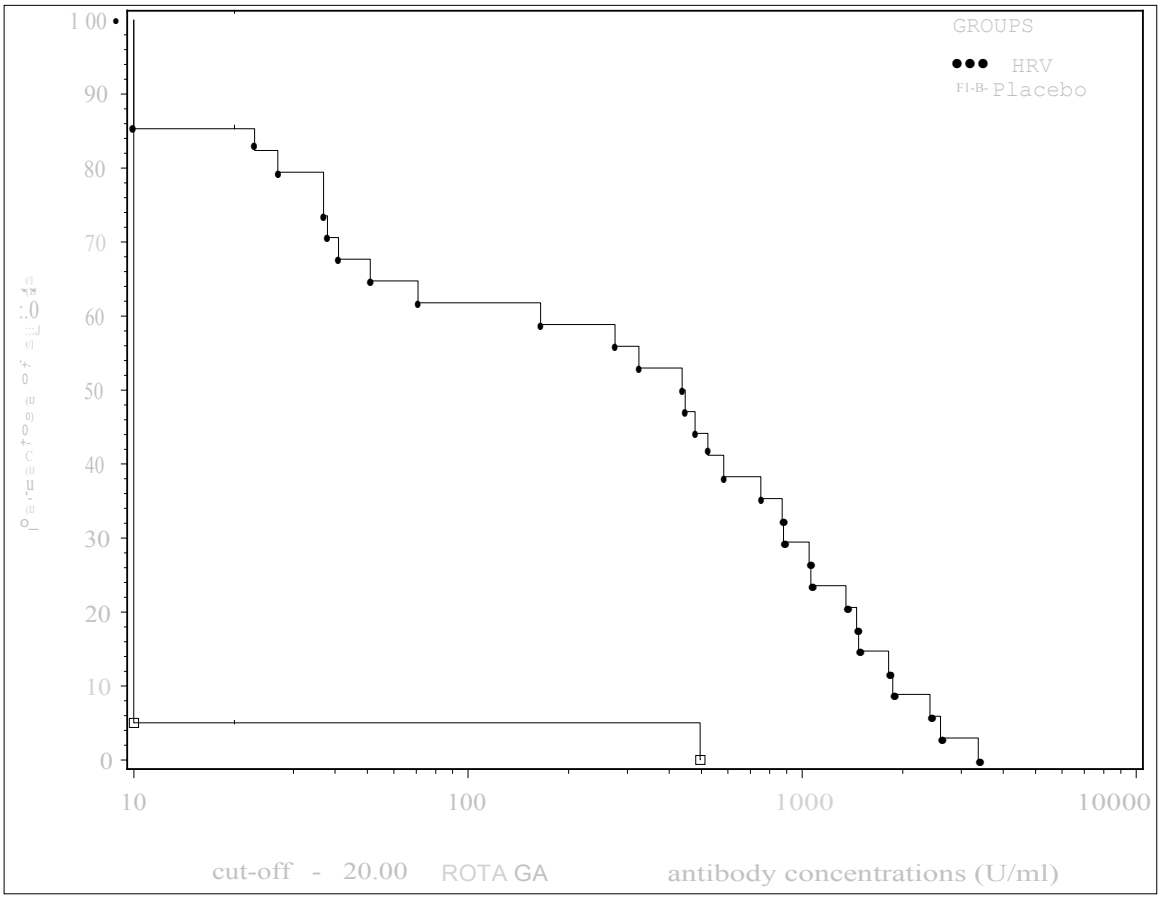
Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age in the primary study
Group B = Subjects who received DTPa-IPV/Hib vaccine at 3, 4, 5 months of age in the primary study
Control = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age in the primary study
Seroprotection=Anti-Poliovirus 1, 2 and 3 antibodies ≥8 ED_{50}
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-BST=Pre-booster vaccination blood sampling time point

Template 15 Difference between groups in percentage of subjects with titre/concentrations equal to or above the proposed cut-off one month after primary vaccination between Form A and Control groups - Inferential analysis (ATP cohort for immunogenicity)

								Difference in percentage (Control minus FormA)		
		Control			FormA				95% CI	
Antibody	**Threshold (unit)**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
Anti-D	0.1 IU/mL	219	219	100	214	214	100	0.00	-2.25	2.30
Anti-T	0.1 IU/mL	219	219	100	214	214	100	0.00	-2.25	2.30
Polio 1	8	219	219	100	214	214	100	0.00	-2.25	2.30
Polio 2	8	219	219	100	214	214	100	0.00	-2.25	2.30
Polio 3	8	219	219	100	214	214	100	0.00	-2.25	2.30
PT	10 IU/mL	219	219	100	214	214	100	0.00	-2.25	2.30
FHA	10 IU/mL	219	219	100	214	214	100	0.00	-2.25	2.30

FormA = DTPa-HBV-IPV/Hib Form A + Prevenar 13 at 2, 3 and 4 months of age
Control = DTPa-HBV-IPV/Hib licensed + Prevenar 13 at 2, 3 and 4 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with concentration and titre within the specified range
97.5% CI = Standardized asymptotic 97.5% confidence interval; LL = lower limit, UL = upper limit

Template 16 Reverse Cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 from a subset of subjects - ATP cohort for immunogenicity



Template 17 Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort)

	dTpaHAV HAVRIX N = 182		dTpaHAV dTpa N = 182		HAVdTpa HAVRIX N = 139		HAVdTpa dTpa N = 139	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0	0	0.0	1	0.5	0	0.0	1	0.7
1	182	100	181	99.5	139	100	138	99.3
Any	182	100	181	99.5	139	100	138	99.3

dTpaHAV = #1 dTpa vaccine(D37750B2)#2 HAV vaccine(DVHA821D2)
HAVdTpa = #1 HAV vaccine(DVHA821D2)#2 dTpa vaccine(D37750B2)
N = number of subjects in each group 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
Data source = Appendix table IG

Template 18 Compliance in returning symptom sheets (Total vaccinated cohort)

Dose	Group	Number of doses	Doses NOT according to protocol	Number of general SS	Compliance % general SS
1	HRV	508	0	508	100
	Placebo	257	0	257	100
2	HRV	499	0	499	100
	Placebo	250	0	250	100
Total	HRV	1007	0	1007	100
	Placebo	507	0	507	100

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100

Template 19 Incidence and nature of symptoms (solicited and unsolicited) reported during the 8-day (Days 0-7) post-vaccination period 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 1	HPV_2D															
	MMR_DTPa															
Dose 2	HPV_2D															
	MMR_DTPa															
Overall/dose	HPV_2D															
	MMR_DTPa															
Overall/subj	HPV_2D															
	MMR_DTPa															

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
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 20 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		HPV_2D					MMR_DTPa				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All										
	Grade 3										
	Medical advice										
Redness (mm)	All										
	>20										
	Medical advice										
Swelling (mm)	All										
	>20										
	Medical advice										

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
N = number of subjects with an administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 21 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		HPV_2D					MMR_DTPa				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										
Dose 2											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										
Overall/dose											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										

		HPV_2D					MMR_DTPa				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										
Overall/subject											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										

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
For each dose and overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 22 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		HPV_2D					MMR_DTPa				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All										
	Grade 3										
	Medical advice										
Redness (mm)	All										
	>20										
	Medical advice										
Swelling (mm)	All										
	>20										
	Medical advice										

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
N = number of subjects with a documented dose
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 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		HPV_2D					MMR_DTPa				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										
Dose 2											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										
Overall/dose											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										

		HPV_2D					MMR_DTPa				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										
Overall/subject											
Each symptom except fever	All										
	Grade 3										
	Related										
	Grade 3 Related										
	Medical advice										
Fever/(Axillary) (°C)	All										
	≥37.5										
	>38.0										
	>38.5										
	>39.0										
	>39.5										
	>40.0										
	Related										
	>38.0 Related										
	>38.5 Related										
	>39.0 Related										
	>39.5 Related										
	>40.0 Related										
	Medical advice										

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
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

Template 24 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

		HPV_2D N =				MMR_DTPa N =			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom									
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)								
Ear and labyrinth disorders (10013993)	Ear pain (10014020)								
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)								
	Abdominal pain upper (10000087)								
	Anal fissure (10002153)								

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 at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 25 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 43-day (Days 0-42) post-vaccination period (Total vaccinated cohort)

		HPV_2D N =				MMR_DTPa N =			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom									
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)								
Ear and labyrinth disorders (10013993)	Ear pain (10014020)								
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)								
	Abdominal pain upper (10000087)								
	Anal fissure (10002153)								

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 administered doses
n (%) = number (percentage) of doses with the symptom
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

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)

Template 27 Listings of SAEs (Total vaccinated cohort)

Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
PP	PPD	37	F	Blinded	Blinded	Infections and infestations	HO	2	177	6	2	N	Recovered/resolved
	PPD	38	F	Blinded	Blinded	Infections and infestations	HO	2	182	10	2	N	Recovered/resolved
	PPD	66	F	Blinded	Blinded	Respiratory, thoracic and mediastinal disorders	HO	2	375	7	2	N	Recovered/resolved
		66		Blinded	Blinded	Infections and infestations	HO	2	375	5	2	N	Recovered/resolved
PP	PPD	78	M	Blinded	Blinded	Infections and infestations	HO	2	467	8	2	N	Recovered/resolved
PP	PPD	56	F	Blinded	Blinded	Infections and infestations	HO	2	299	13	2	N	Recovered/resolved
		56		Blinded	Blinded	Blood and lymphatic system disorders	HO	2	299	133	2	N	Recovered/resolved
	PPD	59	F	Blinded	Blinded	Infections and infestations	HO	2	319	11	2	N	Recovered/resolved
	PPD	73	F	Blinded	Blinded	Infections and infestations	ER	2	417	5	2	N	Recovered/resolved
PPD	PPD	13	M	Blinded	Blinded	Infections and infestations	HO	2	15	17	1	N	Recovered/resolved
		13		Blinded	Blinded	Infections and infestations	HO	2	17	8	2	N	Recovered/resolved
PP	PPD	25	M	Blinded	Blinded	Infections and infestations	HO	2	90	15	2	N	Recovered/resolved
PPD	PPD	24	M	Blinded	Blinded	Musculoskeletal and connective tissue disorders	HO	2	76	31	1	N	Recovered/resolved

HO = hospitalisation
MD = Medical Personnel

Template 28 Number and percentage of doses and of subjects who took at least one concomitant medication during the study period (from Dose 1 till database lock) by type (Total vaccinated cohort)

	HRV					Placebo				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1										
Any	508	165	32.5	28.4	36.7	257	70	27.2	21.9	33.1
Any antipyretic	508	16	3.1	1.8	5.1	257	13	5.1	2.7	8.5
Prophylactic antipyretic	508	0	0.0	0.0	0.7	257	0	0.0	0.0	1.4
Any antibiotic	508	59	11.6	9.0	14.7	257	22	8.6	5.4	12.7
Dose 2										
Any	499	217	43.5	39.1	48.0	250	122	48.8	42.5	55.2
Any antipyretic	499	32	6.4	4.4	8.9	250	21	8.4	5.3	12.6
Prophylactic antipyretic	499	0	0.0	0.0	0.7	250	0	0.0	0.0	1.5
Any antibiotic	499	105	21.0	17.5	24.9	250	51	20.4	15.6	25.9
Overall/dose										
Any	1007	382	37.9	34.9	41.0	507	192	37.9	33.6	42.3
Any antipyretic	1007	48	4.8	3.5	6.3	507	34	6.7	4.7	9.2
Prophylactic antipyretic	1007	0	0.0	0.0	0.4	507	0	0.0	0.0	0.7
Any antibiotic	1007	164	16.3	14.1	18.7	507	73	14.4	11.5	17.8
Overall/subject										
Any	508	300	59.1	54.6	63.4	257	155	60.3	54.0	66.3
Any antipyretic	508	43	8.5	6.2	11.2	257	32	12.5	8.7	17.1
Prophylactic antipyretic	508	0	0.0	0.0	0.7	257	0	0.0	0.0	1.4
Any antibiotic	508	152	29.9	26.0	34.1	257	65	25.3	20.1	31.1

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
Database lock date = 31 Mar 2009

Template 29 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		HPV_2D					MMR_DTPa				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Each symptom except fever	All										
	Grade 3										
	Related										
Fever/(Axillary) (°C)	All										
	>39.0										
	Related										
Dose 2											
Each symptom except fever	All										
	Grade 3										
	Related										
Fever/(Axillary) (°C)	All										
	>39.0										
	Related										
Dose 3											
Each symptom except fever	All										
	Grade 3										
	Related										
Fever/(Axillary) (°C)	All										
	>39.0										
	Related										
Across Doses											
Each symptom except fever	All										
	Grade 3										
	Related										
Fever/(Axillary) (°C)	All										
	>39.0										
	Related										

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
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 30 Number (%) of subjects with serious adverse events from first study vaccination up to Visit 7 including number of events reported (Total vaccinated cohort)

			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 31 Solicited and unsolicited symptoms experienced by at least 5 % of subjects classified by MedDRA Primary System Organ Class and Preferred Term within 31-day (Days 0-30) post-vaccination period after any dose of liquid HRV vaccine and first dose of DPT-IPV vaccine - 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 32 Number of enrolled subjects by age category (Total vaccinated cohort)

		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>