GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, *Boostrix*, administered as a booster dose in healthy Russian subjects aged four years and older.
eTrack study number and Abbreviated Title	201532 [DTPA (BOOSTRIX)-050]
Scope:	All analyses as planned per protocol and for study report.
Date of Statistical Analysis Plan	09-OCT-2017
Co-ordinating author:	PPD (Lead Statistician)
Reviewed by:	PPD (Clinical and Epidemiology R&D Project Leader) PPD, Clinical Research and Development Lead (CRDL) PPD (Study statistician) PPD (peer reviewer statistician) PPD (public disclosure) PPD (Scientific writer) PPD (Lead statistical analyst) PPD (Global Regulatory Affairs) Ivonne PPD and PPD (Safety Physician)
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14April 2017)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF TEMPLATES

PAGE

LIST OF ABBREVIATIONS

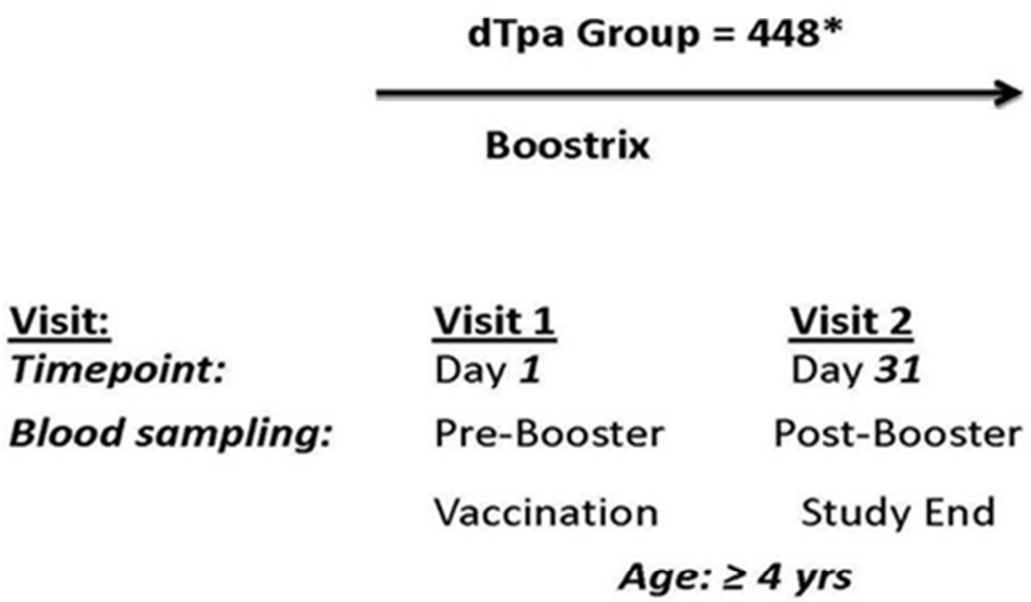
AE	Adverse event
ANOVA	Analysis of Variance
BS	Blood Sample
cDISCI	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EL.U/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
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
ATP	Per Protocol Set
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
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
09-Oct-2017	first version	Amendment 02 Final 1: 07 August 2017

2. STUDY DESIGN



* An equal number of subjects are expected to be recruited in the following age categories: 4-9 years (children), 10-17 years (adolescents), 18-64 years (adults) and ≥65 years (elderly population) in order to evaluate data.

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

- Experimental design: Phase III, open-label, non-randomised, multi-centric, single-country study with a single group.
- Duration of the study:
  - Epoch 001: Primary Epoch starting at Visit 1 (Day 1) and ending at Visit 2 (Day 31)
- Primary Completion Date (PCD): Visit 2 (Day 31)
- End of Study (EoS): Last testing results released of samples collected at Visit 2.
- Study groups: The study group and epoch foreseen in this study is presented in Table 1.

Table 1 Study group and epoch foreseen in the study

Study group	Number of subjects	Age (Min)	Epoch
			Epoch 001
dTpa Group	448	≥4 years	x

Table 2 Study group and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Group
		dTpa Group
Boostrix	dTpa	x

- Control: uncontrolled (in terms of no active comparator).
- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects at Visit 1 (Day 1).
- Treatment allocation: Non-randomised and stratified by age.
- Blinding: open.

Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	open

- Sampling schedule: A blood sample of approximately 5 ml will be collected from all subjects before vaccination (at the Pre-Booster timepoint) and one month after vaccination (Post-Booster timepoint).
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

3. OBJECTIVES

3.1. Primary objectives

- To assess the immune response to the dTpa vaccine in terms of seroprotection status for antibodies against diphtheria and tetanus antigens and in terms of seropositivity status for antibodies against the pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)], one month after vaccination.

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

3.2. Secondary objectives

- To assess the immune response in terms of booster response* to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.
- To assess the immune response in terms of antibody concentrations to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.

- To assess the reactogenicity and safety of Boostrix in terms of solicited symptoms (local and general), unsolicited adverse events (AEs) 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* and anti-tetanus seroprotection status (ie antibody concentrations ≥0.1 IU/ml), one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN seropositivity status (ie antibody concentration is greater than or equal to the assay cut-off value), one month after vaccination.

  *Sera with ELISA concentrations <0.1 IU/ml will be tested for neutralising antibodies using a Vero-cell neutralisation assay.

4.2. Secondary endpoints

- Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.
  - Booster response to Diphtheria and Tetanus antigens is defined as:
    - for subjects with pre-vaccination antibody concentration <0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥0.4 IU/ml, one month after vaccination, and
    - for subjects with pre-vaccination antibody concentration ≥0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
  - Booster response to PT, FHA and PRN antigens is defined as:
    - for subjects with pre-vaccination antibody concentration below the assay cut-off, post-vaccination antibody concentration ≥ four times the assay cut-off,
    - for subjects with pre-vaccination antibody concentration between the assay cut-off and below four times the assay cut-off, post-vaccination antibody concentration ≥ four times the pre-vaccination antibody concentration, and
    - for subjects with pre-vaccination antibody concentration ≥ four times the assay cut-off, post-vaccination antibody concentration ≥ two times the pre-vaccination antibody concentration
- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria anti-tetanus, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.

- Solicited local and general symptoms.
    - Occurrence of each solicited local and general symptom during the 4-day (Day 1-4) follow-up period after vaccination.
    - Occurrence of large swelling reactions during the 4-day (Day 1-4) follow-up period after vaccination.
- Unsolicited adverse events.
    - Occurrence of unsolicited AEs during the 31-day (Day 1-31) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events.
    - Occurrence of SAEs from the vaccination up to study end.

5. ANALYSIS SETS

5.1. Definition

5.1.1. Total vaccinated cohort (TVC)

The TVC will include all subjects with at least one study vaccine administration documented.

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity data are available.

Note that enrolled subjects who gave informed consent or blood sample pre-vaccination but were not vaccinated will be excluded from TVC.

5.1.2. Per protocol cohort for analysis of immunogenicity

The PP cohort for immunogenicity will include all evaluable subjects:

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known and according to the protocol.
- Who have not received a vaccine not specified or forbidden in the protocol.
- Who meet all eligibility criteria.
- Who are within the maximum interval (the interval between Visit 1 and blood sampling at Visit 2, considered for inclusion of a subject will be 21–48 days) allowed as defined in the protocol.

- Who did not receive a product leading to exclusion from a PP analysis (refer to Section 6.7.2 of the protocol, namely
    - Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
    - Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.
    - Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
    - A vaccine not foreseen by the study protocol administered during the period starting from the dose of study vaccine (Day 1) and ending 31 days after the dose of vaccine administration, with the exception of influenza vaccine which is allowed throughout the study period.
    - 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 Summary of Product Characteristics (SmPC) and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
    - Immunoglobulins and/or any blood products administered during the study period.)
- Who did not present with a medical condition leading to exclusion from an PP analysis (refer to Section 6.8 of the protocol, namely subjects will be eliminated from the PP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status).
- For whom data concerning immunogenicity endpoint measures are available post vaccination. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component.

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.

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
1040	Administration of vaccine(s) forbidden in the protocol => o Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period. o A vaccine not foreseen by the study protocol administered during the period starting from the dose of study vaccine (Day 1) and ending 31 days after the dose of vaccine administration, with the exception of influenza vaccine which is allowed throughout the study period. This includes emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) organised by the public health authorities, outside the routine immunisation program.
1070	Study vaccine dose not administered according to protocol => for instance • Route of vaccination is not Intramuscular for Boostrix • Wrong reconstitution of Boostrix before injection
1080	Vaccine temperature deviation => Boostrix vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090	Expired vaccine administered=> Subjects who received an expired Boostrix vaccine
2010	Protocol violation (inclusion/exclusion criteria) => ineligible subject: • age below (excluding) 4 year • Other considerations as stated in section 4.2 – 4.3 in the protocol

2040	Administration of any medication forbidden by the protocol=> • Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed. • Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab). • Immunoglobulins and/or any blood products administered during the study period.)
2070	Concomitant infection not related to the vaccine which may influence immune response = > subject who incurs a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status
2090	Non-compliance with the blood sampling schedule (including wrong and unknown dates) => Blood sample not collected within 21 days-48 days after the Boostrix vaccine.
2100	Essential serological data missing => No serological results at all available post-vaccination (Visit 2)
2120	Obvious incoherence or abnormality or error in data => • BS result available while BS not taken • Post vaccination results below pre-vaccination results for all available assays tested at pre-vaccination ie PT, FHA, PRN, Diphtheria (ELISA), Tetanus

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Not applicable

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

Refer to the protocol deviaito 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 annex 1 and will not be repeated below.

6.1. Demography

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

Demographic characteristics (age at vaccination visit in years, gender and geographical ancestry, body mass index in kg/m^2), cohort description and withdrawal status will be summarised using descriptive statistics:

- Frequency tables will be generated for categorical variable such as centre.
- Mean, median, standard deviation will be provided for continuous data such as age.
- The distribution of subjects based on age stratification will be tabulated (as seen in Table 4).

In addition, the above analysis will also be done for sub-groups based on age as an exploratory analysis.

Table 4 Age stratification

Age groups	Number of subjects
4-9 years	~112
10-17 years	~112
18-64 years	~112
≥65 years	~112

6.1.2. Additional considerations

All demography summaries will be generated for the TVC and ATP cohort. An additional age split will be added in the 4-9 years group to determine the distribution of subjects below 6 year old as solicited symptoms are different (see section 11.2.4).

Number and reason for elimination from ATP will be tabulated.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

Not described in the protocol as a single dose is provided and the number of vaccinated subjects is provided.

6.2.2. Additional considerations

Not applicable.

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the PP cohort for analysis of immunogenicity. If, the percentage of vaccinated subjects with serological results excluded from the PP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the PP analysis.

For all subjects and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination and one month post-vaccination will be calculated with exact 95% CIs.
- GMCs at pre-vaccination and one month post-vaccination will be tabulated with 95% CIs.
- Booster response rate one month post-vaccination will be calculated with exact 95% CIs for diphtheria, tetanus and pertussis antigens.

In addition, the above analysis will also be done based on age stratification (Refer Table 4) as an exploratory analysis.

Finally, antibody concentrations distribution at pre-vaccination and one month post-vaccination will be displayed using reverse cumulative curves (RCC).

Handling of missing data:

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

6.3.2. Additional considerations

Seroprotection and booster response is defined in section 4. The percentage of subjects with ELISA anti-Diphtheria above 0.1 IU/ml or with Vero anti-Diphtheria above 0.01 IU/ml will be summarized at pre and post vaccination. In case subjects with ELISA anti-Diphtheria above 0.1 IU/ml have no result by Vero, the subjects will be treated as censored for Vero anti-Diphtheria and survival method will be used to estimate percentage and associated CI.

A seronegative subject is a subject whose antibody concentration is below the assay cut-off value. A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.

The thresholds defining seropositivity are provided below

Table 5 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/Manufacturer	Unit	*Cut-off*†	Laboratory*
Serum	*Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG*	ELI	NA	IU/ml	0.057	GSK Biologicals or designated laboratory
Serum	*Corynebacterium diphtheriae.Diphtheria Toxoid Ab*	NEU assay on Vero cells**	NA	IU/ml	0.004	GSK Biologicals or designated laboratory
Serum	*Clostridium tetani.Tetanus Toxoid Ab.IgG*	ELI	NA	IU/ml	0.043	GSK Biologicals or designated laboratory
Serum	*Bordetella pertussis.Pertussis Toxin Ab.IgG*	ELI	NA	IU/ml	2.693	GSK Biologicals or designated laboratory
Serum	*Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG*	ELI	NA	IU/ml	2.046	GSK Biologicals or designated laboratory
Serum	*Bordetella pertussis.Pertactin Ab.IgG*	ELI	NA	IU/ml	2.187	GSK Biologicals or designated laboratory

ELI: ELISA
NEU: Neutralisation assay
NA: Not Applicable
IU/ml: International Units per millilitre
†Assays for diphtheria, tetanus and pertussis were re-developed and re-validated as per most recent CBER recommendations (Guidance for Industry "Bioanalytical Method Validation" from September 2013). The new assay cut-off's that apply are listed in the table.
*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium and Wavre, Belgium.
**Test on Vero-cells will be performed on pre- and post-vaccination samples with concentrations <0.1 IU/ml by ELISA.

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

The analysis will be based on the TVC.

- The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 1-4) follow-up period after booster vaccination will be tabulated. 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 during the 4-day follow-up period after vaccination will be reported per 0.5°C cumulative increments.
  - In addition, the above analysis will also be done for sub groups based on age stratification (Refer Table 4) as an exploratory analysis.
- The percentage of subjects 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 (Day 1-4) follow-up period after booster

vaccination will be tabulated with exact 95% CI after booster vaccination. 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 consultation and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.

- The percentage of subjects who started to receive at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day (Day 1-4) and 31-day (Day 1-31) follow-up period after vaccination will be tabulated with exact 95% CI.
- The verbatim reports of unsolicited AEs will be reviewed by a clinical research and development lead 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 the 31-day (Day 1-31) follow-up period after booster dose with its exact 95% CI will be tabulated by Preferred Term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.
- Any large injection site reaction (for subjects <6 years of age defined as a swelling with a diameter of >50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm, noticeable diffuse swelling or noticeable increase in limb circumference) onset during the 4-day (Day 1-4) follow-up period after vaccination will be described in detail.
- SAEs and withdrawal due to AEs and SAEs 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 symptoms and unsolicited adverse event will also be done for medically attended symptom/adverse event and for grade 3 causally related AE.

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

Analysis of the single booster dose will be performed at the end of the study when all data are available. An integrated clinical study report containing all data will be written and made available to the investigators.

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**
Final	E1_01	SR	Yes	Yes	TFL TOC

8.3. Statistical considerations for interim analyses

Not applicable

9. CHANGES FROM PLANNED ANALYSES

Not applicable

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

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

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

The following group 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 Group	Boostrix

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].

If some samples with anti-D concentrations < 0.1 IU/mL cannot be retested by VERO, VERO will be treated as left censored at 0.1 IU/mL and the Greenwoood formula for censored data will be used to estimate the percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥0.01 IU/mL by VERO and its associated CI .

The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.

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. 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.

11.2.3. Immunogenicity

- 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.

11.2.4. 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:

- Subjects who documented the absence of a solicited symptom will be considered not having that symptom.
- 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 without having recorded any daily measurement will be considered as having that symptom (at the lowest intensity).
- Intensity of the following solicited AEs will be assessed as described in Table 6 and below

Table 6 Intensity scales to be used by the parent(s)/LAR(s) for solicited symptoms during the solicited follow-up period

Toddler/Child (<6 years)		
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
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 ≥ 38.0°C. The preferred location for measuring temperature in this study will be the axilla.

Table 7 Intensity scales for solicited symptoms in adults and children of six years of age or more

Adult/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
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
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

***** Fever is defined as temperature ≥ 38.0°C. The preferred location for measuring temperature in this study will be the axilla.

The maximum intensity of local injection site redness/swelling for toddlers and children <6 years of age 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 local injection site redness/swelling for adults and children ≥6 years of age will be scored at GSK Biologicals as follows:

0	Absent
1	≤20 mm
2	>20 mm and ≤50 mm
3	>50 mm

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

0	*<38 ℃*
1	*≥38.0 ℃ to ≤39.0 ℃*
2	*>39.0 ℃ to ≤40.0 ℃*
3	*>40.0 ℃*

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**
Headache	10019211	Drowsiness
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	
Drowsiness	10013649	Drowsiness
Fever	10016558	Fever
Irritability/Fussiness	10022998	Irritability
Loss of appetite	10003028	Appetite lost
Pain at injection site	10022086	Injection site pain
Redness at injection site	10022098	Redness at injection site
Swelling at injection site	10053425	Swelling at injection site

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used.

The data display, title and footnote are for illustration purpose and will be adapted to the study specificity such as one group and one dose for the study.

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 (Total Vaccinated Cohort)

	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 (Total Vaccinated Cohort)

	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 (Total Vaccinated Cohort)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
HRV Liq	VISIT 1	508		
			no. PP	CONSENT WITHDRAWAL
			no. PP	CONSENT WITHDRAWAL
			no. PP	CONSENT WITHDRAWAL
			no. PP	CONSENT WITHDRAWAL
	VISIT 2	504		
			no. PPD	CONSENT WITHDRAWAL
			no. PP	CONSENT WITHDRAWAL
			no. PP	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. PP	CONSENT WITHDRAWAL
			no. PP	MIGRATION FROM STUDY AREA
			no. PP	MIGRATION FROM STUDY AREA
	VISIT 4	492		
HRV Lyo	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. PP	LOST TO FOLLOW-UP
			no. PP	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 (Total Vaccinated Cohort)

		Age	VAC_1-SER_2	
Group		**Protocol**	**Protocol**	**Adapted**
		from 10 to 15 year	from 30 to 48 days	from 21 to 48 days
dTpaNew Group	N	335	329	329
	n	0	11	8
	%	0.0	3.3	2.4
	range	10 to 15	28 to 74	28 to 74
dTpaPre Group	N	336	329	329
	n	0	10	8
	%	0.0	3.0	2.4
	range	10 to 15	29 to 95	29 to 95

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
dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
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
VAC = vaccination
SER = Blood Sampling

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

		dTpaNew Group N = 335		dTpaPre Group N = 336		Total N = 671	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	11.9	-	11.9	-	11.9	-
	SD	1.59	-	1.61	-	1.60	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	10	-	10	-	10	-
	Maximum	15	-	15	-	15	-
Gender	Female	179	53.4	178	53.0	357	53.2
	Male	156	46.6	158	47.0	314	46.8
Geographic Ancestry	African Heritage / African American	1	0.3	1	0.3	2	0.3
	American Indian or Alaskan Native	146	43.6	149	44.3	295	44.0
	White - Arabic / North African Heritage	1	0.3	0	0.0	1	0.1
	White - Caucasian / European Heritage	9	2.7	12	3.6	21	3.1
	Other (Hispanic)	178	53.1	174	51.8	352	52.5

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = total number of subjects
n(%) = Number(percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Template 7 Summary of vital signs characteristics (Total Vaccinated Cohort)

		dTpaNew Group (N = 335)	dTpaPre Group (N = 336)	Total (N = 671)
Characteristics	**Parameters**	**Value**	**Value**	**Value**
Height (km)	Mean	152.6	151.5	152.1
	SD	10.48	10.44	10.47
	Median	152.0	151.5	152.0
	Minimum	112.0	126.0	112.0
	Maximum	189.0	187.0	189.0
	Unknown	0	0	0
Weight (kg)	Mean	49.7	48.8	49.2
	SD	13.23	13.61	13.42
	Median	47.0	47.1	47.0
	Minimum	28.0	19.4	19.4
	Maximum	99.0	110.0	110.0
	Unknown	0	0	0
BMI (kg/m²)	Mean	21.1	20.9	21.0
	SD	3.92	3.91	3.92
	Median	20.6	20.4	20.4
	Minimum	11.9	9.8	9.8
	Maximum	33.5	34.0	34.0
	Unknown	0	0	0

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Height (cm) = Height expressed in centimeters
Weight (kg) = Weight expressed in kilograms
BMI (kg/m^2) = Body Mass Index expressed in kilograms per meter square

Template 8 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 9 Seropositivity and seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies before and one month after the booster vaccination (ATP cohort for immunogenicity)

				≥ assay cut-off*				≥ 0.1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-diphtheria	dTpaNew Group	PRE	321	284	88.5	84.5	91.8	83	25.9	21.2	31.0	0.472	0.403	0.553
		POST	321	320	99.7	98.3	100	315	98.1	96.0	99.3	6.784	6.178	7.450
	dTpaPre Group	PRE	319	286	89.7	85.8	92.8	89	27.9	23.0	33.2	0.456	0.392	0.530
		POST	319	319	100	98.9	100	310	97.2	94.7	98.7	6.493	5.915	7.128
anti-tetanus	dTpaNew Group	PRE	321	311	96.9	94.3	98.5	151	47.0	41.5	52.7	0.956	0.835	1.095
		POST	321	321	100	98.9	100	321	100	98.9	100	18.937	17.313	20.713
	dTpaPre Group	PRE	319	314	98.4	96.4	99.5	143	44.8	39.3	50.5	0.899	0.789	1.026
		POST	319	319	100	98.9	100	319	100	98.9	100	18.515	16.851	20.342

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
Seroprotection=anti-diphtheria and anti-tetanus antibody concentration ≥0.1 IU/mL
*Assay cut-off is 0.057 IU/mL and 0.043 IU/mL for anti-diphtheria and anti-tetanus respectively
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n(%)=number(percentage) of subjects with antibody concentrations above the specified cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE=Pre-booster blood sampling time point
POST=Post-booster blood sampling time point

Template 10 Booster responses for anti-PT, anti-FHA and anti-PRN antibody concentration one month after the booster vaccination (ATP cohort for immunogenicity)

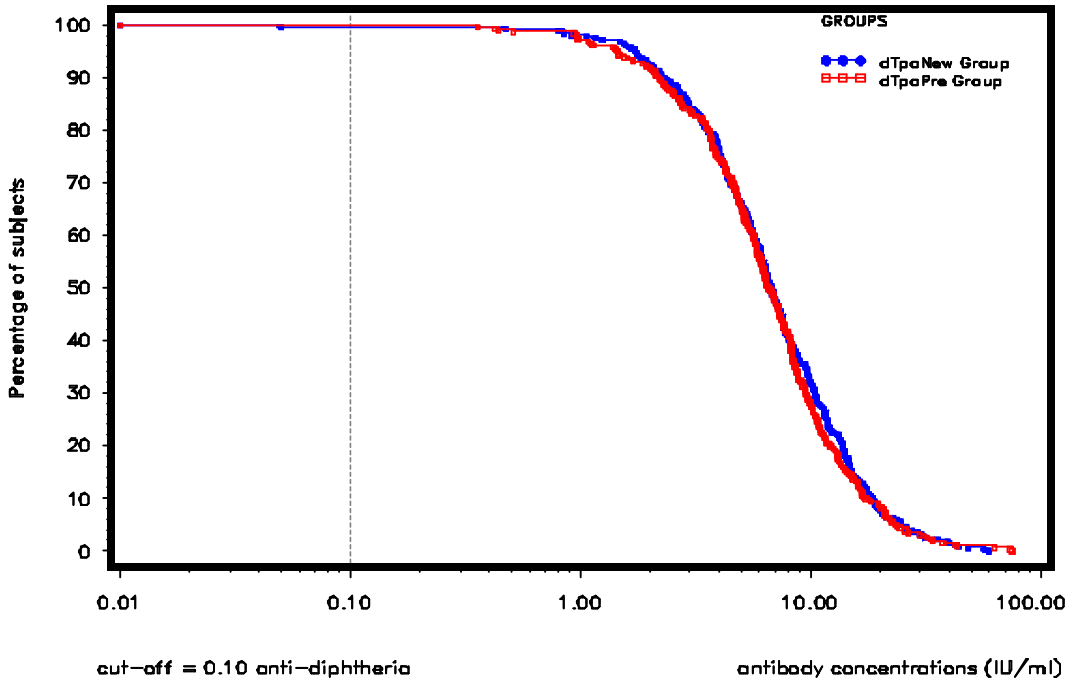
				Booster response			
						95% CI	
Antibody	**Group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
anti-PT	dTpaNew Group	S-	142	135	95.1	90.1	98.0
		S+ (< 4*assay cut-off)	104	103	99.0	94.8	100
		S+ (≥4*assay cut-off)	71	60	84.5	74.0	92.0
		Total	317	298	94.0	90.8	96.4
	dTpaPre Group	S-	143	131	91.6	85.8	95.6
		S+ (<4*assay cut-off)	114	112	98.2	93.8	99.8
		S+ (≥4*assay cut-off)	61	52	85.2	73.8	93.0
		Total	318	295	92.8	89.3	95.4
anti-FHA	dTpaNew Group	S-	6	6	100	54.1	100
		S+ (<4*assay cut-off)	57	57	100	93.7	100
		S+ (≥4*assay cut-off)	251	242	96.4	93.3	98.3
		Total	314	305	97.1	94.6	98.7
	dTpaPre Group	S-	5	5	100	47.8	100
		S+ (<4*assay cut-off)	55	55	100	93.5	100
		S+ (≥4*assay cut-off)	255	244	95.7	92.4	97.8
		Total	315	304	96.5	93.8	98.2
anti-PRN	dTpaNew Group	S-	52	50	96.2	86.8	99.5
		S+ (<4*assay cut-off)	152	151	99.3	96.4	100
		S+ (≥4*assay cut-off)	117	114	97.4	92.7	99.5
		Total	321	315	98.1	96.0	99.3
	dTpaPre Group	S-	47	47	100	92.5	100
		S+ (<4*assay cut-off)	159	159	100	97.7	100
		S+ (≥4*assay cut-off)	112	111	99.1	95.1	100
		Total	318	317	99.7	98.3	100

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
S- = Initially seronegative subjects prior to vaccination
S+ = Initially seropositive subjects prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
S- = seronegative subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
S+ = seropositive (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
Booster response to PT, FHA and PRN antigens is defined as:

- initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- initially seropositive subjects with anti-body concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination
- initially seropositive subjects with anti-body concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination

Assay cut-off is 2.693 IU/mL, 2.046 IU/mL and 2.187 IU/mL for anti-PT, FHA and PRN respectively
N = number of subjects with both pre- and post-vaccination results available
n(%) = number(percentage) of subjects with a booster response
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 11 Reverse cumulative curve for anti-diphtheria antibody concentration one month after the booster vaccination (ATP cohort for immunogenicity)



dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation

Template 12 Seroprotection rate for anti-Diphtheria antibody concentration by ELISA and VERO NEUTRALISATION (ATP cohort)

			ELISA concentrations below the 0.1 IU/ml		Neutra concentrations below the 0.01 IU/ml among subjects with ELISA concentrations below the 0.1 IU/ml		Neutra concentrations below the 0.01 IU/ml among subjects with ELISA results		Estimated proportion of protected subjects (SP) and its 95% CI		
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
(each group)	Pre										
	post										

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
N = number of subjects tested by ELISA
N' = number of subjects with ELISA concentrations below the 0.1 IU/ml who were tested by Vero
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ml for ELISA and 0.01 IU/ml for VERO) n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-Diphtheria
Overall = based on both the ELISA and the Vero-cell neutralisation testing
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Pre= blood sampling, at Month 0 before vaccination
post= blood sampling, one motnh after vaccination
SP= proportion of subjects with either ELISA concentrations above 0.1 IU/ml or Neutra concentration above 0.01 IU/mL

Template 13 Compliance in returning symptom information (Total Vaccinated Cohort)

Group	**Number of doses**	**Doses NOT according to protocol**	**Number of general SS**	**Compliance % general SS**	**Number of local SS**	**Compliance % local SS**
dTpaNew Group	335	0	330	98.5	330	98.5
dTpaPre Group	336	1	329	97.9	329	97.9

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Template 14 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**
dTpaNew Group	335	264	78.8	74.0	83.1	335	134	40.0	34.7	45.5	335	250	74.6	69.6	79.2
dTpaPre Group	336	279	83.0	78.6	86.9	336	151	44.9	39.5	50.4	336	264	78.6	73.8	82.8

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the administered dose
n(%)= number(percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 15 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) period after vaccination following each dose and overall (Total Vaccinated Cohort)

		dTpaNew Group					dTpaPre Group				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	330	237	71.8	66.6	76.6	329	248	75.4	70.4	79.9
	Grade 3	330	24	7.3	4.7	10.6	329	20	6.1	3.8	9.2
	Medical advice	330	0	0.0	0.0	1.1	329	0	0.0	0.0	1.1
Redness (mm)	All	330	113	34.2	29.1	39.6	329	94	28.6	23.8	33.8
	Grade 3	330	4	1.2	0.3	3.1	329	1	0.3	0.0	1.7
	Medical advice	330	0	0.0	0.0	1.1	329	0	0.0	0.0	1.1
Swelling (mm)	All	330	98	29.7	24.8	34.9	329	90	27.4	22.6	32.5
	Grade 3	330	6	1.8	0.7	3.9	329	5	1.5	0.5	3.5
	Medical advice	330	0	0.0	0.0	1.1	329	0	0.0	0.0	1.1

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the 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 16 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

		dTpaNew Group					dTpaPre Group				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All	330	83	25.2	20.6	30.2	329	86	26.1	21.5	31.2
	Grade 3	330	7	2.1	0.9	4.3	329	4	1.2	0.3	3.1
	Related	330	77	23.3	18.9	28.3	329	83	25.2	20.6	30.3
	Medical advice	330	1	0.3	0.0	1.7	329	1	0.3	0.0	1.7
Gastrointestinal	All	330	32	9.7	6.7	13.4	329	42	12.8	9.4	16.9
	Grade 3	330	3	0.9	0.2	2.6	329	3	0.9	0.2	2.6
	Related	330	29	8.8	6.0	12.4	329	40	12.2	8.8	16.2
	Medical advice	330	2	0.6	0.1	2.2	329	1	0.3	0.0	1.7
Headache	All	330	88	26.7	22.0	31.8	329	108	32.8	27.8	38.2
	Grade 3	330	5	1.5	0.5	3.5	329	3	0.9	0.2	2.6
	Related	330	80	24.2	19.7	29.2	329	103	31.3	26.3	36.6
	Medical advice	330	2	0.6	0.1	2.2	329	1	0.3	0.0	1.7
Temperature/(Axillary) (°C)	All	330	9	2.7	1.3	5.1	329	6	1.8	0.7	3.9
	≥37.5	330	9	2.7	1.3	5.1	329	6	1.8	0.7	3.9
	>38.0	330	5	1.5	0.5	3.5	329	1	0.3	0.0	1.7
	>38.5	330	3	0.9	0.2	2.6	329	1	0.3	0.0	1.7
	>39.0	330	2	0.6	0.1	2.2	329	0	0.0	0.0	1.1
	Related	330	7	2.1	0.9	4.3	329	6	1.8	0.7	3.9
	Medical advice	330	2	0.6	0.1	2.2	329	0	0.0	0.0	1.1

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the 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
Related = Symptoms which is assessed by the investigator as related to vaccination
Grade3*Related = Grade 3 symptom which is assessed by the investigator as related to vaccination
Grade 3 For Headache: Headache that prevented normal activity
For Fatigue: Fatigue that prevented normal activity
For Gastrointestinal symptoms: Gastrointestinal symptoms that prevented normal activity
For Fever: >39.0 °C

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 (Total Vaccinated Cohort)

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

Primary System Organ Class (CODE)	Preferred Term (CODE)	HRV LIQ N = 298				HRV LIQ N = 302				HRV LIQ N = 300			
				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pneumonia (10035664)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Respiratory tract infection (10062352)	3	1.0	0.2	2.9	2	0.7	0.1	2.4	0	0.0	0.0	1.2
	Respiratory tract infection viral (10062106)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rhinitis (10039083)	2	0.7	0.1	2.4	1	0.3	0.0	1.8	3	1.0	0.2	2.9
	Upper respiratory tract infection (10046306)	2	0.7	0.1	2.4	5	1.7	0.5	3.8	7	2.3	0.9	4.7
	Varicella (10046980)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	2	0.7	0.1	2.4
Psychiatric disorders (10037175)	Crying (10011469)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	6	2.0	0.7	4.3
	Nasal congestion (10028735)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Rales (10037833)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Eczema (10014184)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rash (10037844)	2	0.7	0.1	2.4	0	0.0	0.0	1.2	0	0.0	0.0	1.2

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

Template 18 Number (%) of subjects with serious adverse events from first study vaccination up to Visit 3 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 19 Subjects with Serious Adverse Events reported up to Visit 2 (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	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 20 Number and percentage of subjects who started at least one concomitant medication from Day 0 to Day 7 (Total Vaccinated Cohort)

	dTpaNew Group					dTpaPre Group				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Any	335	41	12.2	8.9	16.2	336	43	12.8	9.4	16.8
Any antipyretic	335	37	11.0	7.9	14.9	336	41	12.2	8.9	16.2
Prophylactic antipyretic	335	2	0.6	0.1	2.1	336	2	0.6	0.1	2.1

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the administered dose
n(%)= number(percentage) of subjects who started to take the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 21 Solicited and Unsolicited symptoms experienced by subjects classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period - 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 22 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 23 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 24 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 25 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 26 Percentage of subjects with large injection site reaction during the 4-day (Days 0-3) period after Boostrix (Total Vaccinated Cohort)

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 = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, *Boostrix*, administered as a booster dose in healthy Russian subjects aged four years and older.
eTrack study number and Abbreviated Title	201532 [DTPA (BOOSTRIX)-050]
Scope:	All analyses as planned per protocol and for study report.
Date of Statistical Analysis Plan	Amendment 1 Final: 10 March 2019
Co-ordinating author:	PPD (Lead Statistician) PPD (Study statistician)
First version reviewed by:	PPD (Clinical and Epidemiology R&D Project Leader) PPD, Clinical Research and Development Lead (CRDL) PPD (Study statistician) PPD (peer reviewer statistician) PPD (public disclosure) PPD (Scientific writer) PPD (Lead statistical analyst) PPD (Global Regulatory Affairs) PPD and PPD (Safety Physician)

Amendment 1 reviewed by:	PPD (Clinical and Epidemiology R&D Project Leader) PPD, Clinical Research and Development Lead (CRDL) PPD (Lead statistician) PPD (Scientific writer) PPD (Lead stat analyst)
Approved by:	PPD (Clinical and Epidemiology R&D Project Leader) PPD, Clinical Research and Development Lead (CRDL) PPD (Study statistician) PPD (Lead Statistician) PPD (Lead stat analyst, approver) PPD (Scientific writer)

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

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF TEMPLATES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of Variance
ATP	Per Protocol Set
BS	Blood Sample
cDISCI	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EL.U/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
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
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation

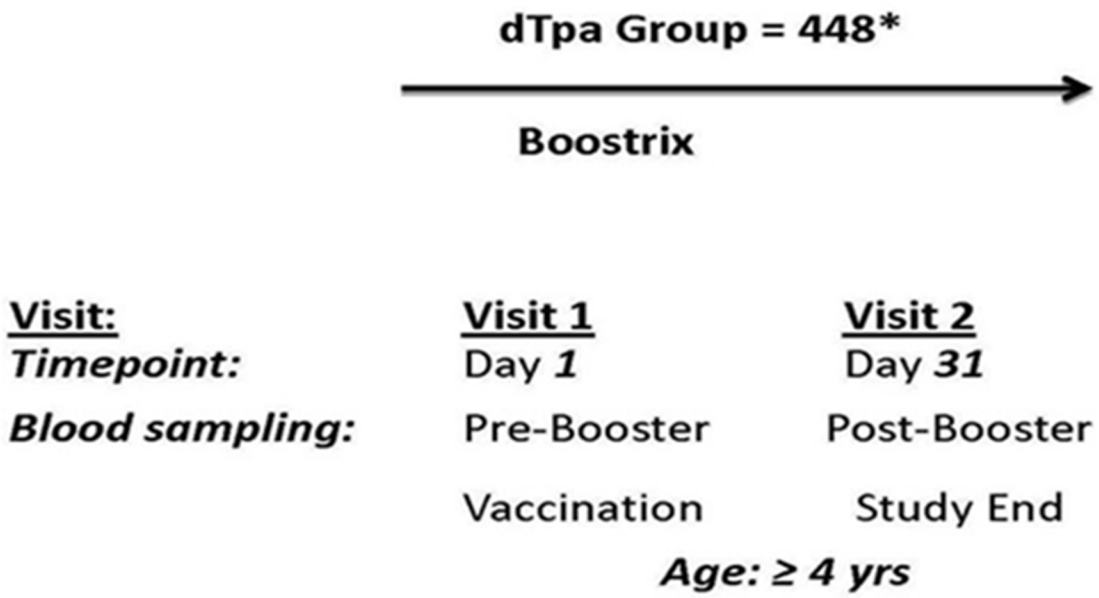
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
09-OCT-2017	first version	Amendment 02 Final 1: 07-AUG-2017
10-MAR-2019	Amendment 1*	Amendment 02 Final 1: 07-AUG-2017

* summary of GMC fold increase from pre to post vaccination has been added.

2. STUDY DESIGN



* An equal number of subjects are expected to be recruited in the following age categories: 4-9 years (children), 10-17 years (adolescents), 18-64 years (adults) and ≥65 years (elderly population) in order to evaluate data.

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

- Experimental design: Phase III, open-label, non-randomised, multi-centric, single-country study with a single group.
- Duration of the study:
  - Epoch 001: Primary Epoch starting at Visit 1 (Day 1) and ending at Visit 2 (Day 31)
- Primary Completion Date (PCD): Visit 2 (Day 31)
- End of Study (EoS): Last testing results released of samples collected at Visit 2.
- Study groups: The study group and epoch foreseen in this study is presented in Table 1.

Table 1 Study group and epoch foreseen in the study

Study group	Number of subjects	Age (Min)	Epoch
			Epoch 001
dTpa Group	448	≥4 years	x

Table 2 Study group and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Group
		dTpa Group
Boostrix	dTpa	x

- Control: uncontrolled (in terms of no active comparator).
- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects at Visit 1 (Day 1).
- Treatment allocation: Non-randomised and stratified by age.
- Blinding: open.

Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	open

- Sampling schedule: A blood sample of approximately 5 ml will be collected from all subjects before vaccination (at the Pre-Booster timepoint) and one month after vaccination (Post-Booster timepoint).
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

3. OBJECTIVES

3.1. Primary objectives

- To assess the immune response to the dTpa vaccine in terms of seroprotection status for antibodies against diphtheria and tetanus antigens and in terms of seropositivity status for antibodies against the pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)], one month after vaccination.

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

3.2. Secondary objectives

- To assess the immune response in terms of booster response* to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.
- To assess the immune response in terms of antibody concentrations to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.
- To assess the reactogenicity and safety of Boostrix in terms of solicited symptoms (local and general), unsolicited adverse events (AEs) 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* and anti-tetanus seroprotection status (ie antibody concentrations ≥0.1 IU/ml), one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN seropositivity status (ie antibody concentration is greater than or equal to the assay cut-off value), one month after vaccination.

  *Sera with ELISA concentrations <0.1 IU/ml will be tested for neutralising antibodies using a Vero-cell neutralisation assay.

4.2. Secondary endpoints

- Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.
  - Booster response to Diphtheria and Tetanus antigens is defined as:
    - for subjects with pre-vaccination antibody concentration <0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥0.4 IU/ml, one month after vaccination, and

  - for subjects with pre-vaccination antibody concentration ≥0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.

- Booster response to PT, FHA and PRN antigens is defined as:
  - for subjects with pre-vaccination antibody concentration below the assay cut-off, post-vaccination antibody concentration ≥ four times the assay cut-off,
  - for subjects with pre-vaccination antibody concentration between the assay cut-off and below four times the assay cut-off, post-vaccination antibody concentration ≥ four times the pre-vaccination antibody concentration, and
  - for subjects with pre-vaccination antibody concentration ≥ four times the assay cut-off, post-vaccination antibody concentration ≥ two times the pre-vaccination antibody concentration

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria anti-tetanus, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom during the 4-day (Day 1-4) follow-up period after vaccination.
  - Occurrence of large swelling reactions during the 4-day (Day 1-4) follow-up period after vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs during the 31-day (Day 1-31) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events.
  - Occurrence of SAEs from the vaccination up to study end.

5. ANALYSIS SETS

5.1. Definition

5.1.1. Total vaccinated cohort (TVC)

The TVC will include all subjects with at least one study vaccine administration documented.

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity data are available.

Note that enrolled subjects who gave informed consent or blood sample pre-vaccination but were not vaccinated will be excluded from TVC.

5.1.2. Per protocol cohort for analysis of immunogenicity

The PP cohort for immunogenicity will include all evaluable subjects:

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known and according to the protocol.
- Who have not received a vaccine not specified or forbidden in the protocol.
- Who meet all eligibility criteria.
- Who are within the maximum interval (the interval between Visit 1 and blood sampling at Visit 2, considered for inclusion of a subject will be 21–48 days) allowed as defined in the protocol.
- Who did not receive a product leading to exclusion from a PP analysis (refer to Section 6.7.2 of the protocol, namely
  - Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
  - Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.
  - Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
  - A vaccine not foreseen by the study protocol administered during the period starting from the dose of study vaccine (Day 1) and ending 31 days after the dose of vaccine administration, with the exception of influenza vaccine which is allowed throughout the study period.

  - 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 Summary of Product Characteristics (SmPC) and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
  - Immunoglobulins and/or any blood products administered during the study period.)

- Who did not present with a medical condition leading to exclusion from an PP analysis (refer to Section 6.8 of the protocol, namely subjects will be eliminated from the PP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status).
- For whom data concerning immunogenicity endpoint measures are available post vaccination. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component.

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.

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
1040	Administration of vaccine(s) forbidden in the protocol => • Any 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 the dose of study vaccine (Day 1) and ending 31 days after the dose of vaccine administration, with the exception of influenza vaccine which is allowed throughout the study period. This includes emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) organised by the public health authorities, outside the routine immunisation program.
1070	Study vaccine dose not administered according to protocol => for instance • Route of vaccination is not Intramuscular for Boostrix • Wrong reconstitution of Boostrix before injection
1080	Vaccine temperature deviation => Boostrix vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090	Expired vaccine administered=> Subjects who received an expired Boostrix vaccine
2010	Protocol violation (inclusion/exclusion criteria) => ineligible subject: • age below (excluding) 4 year • Other considerations as stated in section 4.2 – 4.3 in the protocol

2040	• Administration of any medication forbidden by the protocol=> – Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed. – Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab). – Immunoglobulins and/or any blood products administered during the study period.)
2070	Concomitant infection not related to the vaccine which may influence immune response = > subject who incurs a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status
2090	Non-compliance with the blood sampling schedule (including wrong and unknown dates) => Blood sample not collected within 21 days-48 days after the Boostrix vaccine.
2100	Essential serological data missing => No serological results at all available post-vaccination (Visit 2)
2120	Obvious incoherence or abnormality or error in data => • BS result available while BS not taken • Post vaccination results below pre-vaccination results for all available assays tested at pre-vaccination ie PT, FHA, PRN, Diphtheria (ELISA), Tetanus

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Not applicable

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

Refer to the protocol deviaito 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

Demographic characteristics (age at vaccination visit in years, gender and geographical ancestry, body mass index in kg/m^2), cohort description and withdrawal status will be summarised using descriptive statistics:

- Frequency tables will be generated for categorical variable such as centre.
- Mean, median, standard deviation will be provided for continuous data such as age.
- The distribution of subjects based on age stratification will be tabulated (as seen in Table 4).

In addition, the above analysis will also be done for sub-groups based on age as an exploratory analysis.

Table 4 Age stratification

Age groups	Number of subjects
4-9 years	~112
10-17 years	~112
18-64 years	~112
≥65 years	~112

6.1.2. Additional considerations

All demography summaries will be generated for the TVC and ATP cohort. An additional age split will be added in the 4-9 years group to determine the distribution of subjects below 6 year old as solicited symptoms are different (see section 11.2.4).

Number and reason for elimination from ATP will be tabulated.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

Not described in the protocol as a single dose is provided and the number of vaccinated subjects is provided.

6.2.2. Additional considerations

Not applicable.

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the PP cohort for analysis of immunogenicity. If, the percentage of vaccinated subjects with serological results excluded from the PP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the PP analysis.

For all subjects and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination and one month post-vaccination will be calculated with exact 95% CIs.
- GMCs at pre-vaccination and one month post-vaccination will be tabulated with 95% CIs.
- Booster response rate one month post-vaccination will be calculated with exact 95% CIs for diphtheria, tetanus and pertussis antigens.

In addition, the above analysis will also be done based on age stratification (Refer Table 4) as an exploratory analysis.

Finally, antibody concentrations distribution at pre-vaccination and one month post-vaccination will be displayed using reverse cumulative curves (RCC).

Handling of missing data:

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

6.3.2. Additional considerations

Increase in GMC from pre-vaccination to post-vaccination will be computed with 95% CI.

Seroprotection and booster response is defined in section 4. The percentage of subjects with ELISA anti-Diphtheria above 0.1 IU/ml or with Vero anti-Diphtheria above 0.01 IU/ml will be summarized at pre and post vaccination. In case subjects with ELISA anti-Diphtheria above 0.1 IU/ml have no result by Vero, the subjects will be treated as censored for Vero anti-Diphtheria and survival method will be used to estimate percentage and associated CI.

A seronegative subject is a subject whose antibody concentration is below the assay cut-off value. A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.

The thresholds defining seropositivity are provided below

Table 5 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/Manufacturer	Unit	*Cut-off*†	Laboratory*
Serum	*Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG*	ELI	NA	IU/ml	0.057	GSK Biologicals or designated laboratory
Serum	*Corynebacterium diphtheriae.Diphtheria Toxoid Ab*	NEU assay on Vero cells**	NA	IU/ml	0.004	GSK Biologicals or designated laboratory
Serum	*Clostridium tetani.Tetanus Toxoid Ab.IgG*	ELI	NA	IU/ml	0.043	GSK Biologicals or designated laboratory
Serum	*Bordetella pertussis.Pertussis Toxin Ab.IgG*	ELI	NA	IU/ml	2.693	GSK Biologicals or designated laboratory
Serum	*Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG*	ELI	NA	IU/ml	2.046	GSK Biologicals or designated laboratory
Serum	*Bordetella pertussis.Pertactin Ab.IgG*	ELI	NA	IU/ml	2.187	GSK Biologicals or designated laboratory

ELI: ELISA
NEU: Neutralisation assay
NA: Not Applicable
IU/ml: International Units per millilitre
†Assays for diphtheria, tetanus and pertussis were re-developed and re-validated as per most recent CBER recommendations (Guidance for Industry "Bioanalytical Method Validation" from September 2013). The new assay cut-off's that apply are listed in the table.
*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium and Wavre, Belgium.
**Test on Vero-cells will be performed on pre- and post-vaccination samples with concentrations <0.1 IU/ml by ELISA.

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

The analysis will be based on the TVC.

- The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 1-4) follow-up period after booster vaccination will be tabulated. 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 during the 4-day follow-up period after vaccination will be reported per 0.5°C cumulative increments.
  - In addition, the above analysis will also be done for sub groups based on age stratification (Refer Table 4) as an exploratory analysis.
- The percentage of subjects 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 (Day 1-4) follow-up period after booster vaccination will be tabulated with exact 95% CI after booster vaccination. 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 consultation and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.
- The percentage of subjects who started to receive at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day (Day 1-4) and 31-day (Day 1-31) follow-up period after vaccination will be tabulated with exact 95% CI.
- The verbatim reports of unsolicited AEs will be reviewed by a clinical research and development lead 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 the 31-day (Day 1-31) follow-up period after booster dose with its exact 95% CI will be tabulated by Preferred Term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.
- Any large injection site reaction (for subjects <6 years of age defined as a swelling with a diameter of >50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm, noticeable diffuse swelling or noticeable increase in limb circumference) onset during the 4-day (Day 1-4) follow-up period after vaccination will be described in detail.
- SAEs and withdrawal due to AEs and SAEs 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 symptoms and unsolicited adverse event will also be done for medically attended symptom/adverse event and for grade 3 causally related AE.

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

Analysis of the single booster dose will be performed at the end of the study when all data are available. An integrated clinical study report containing all data will be written and made available to the investigators.

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**
Final	E1_01	SR	Yes	Yes	TFL TOC

8.3. Statistical considerations for interim analyses

Not applicable

9. CHANGES FROM PLANNED ANALYSES

Template 27 is a new addition to the SAP as per the dry run meeting minutes.

As per the dry run meeting minutes the TFL TOC is update by adding few additional tables, and more details are available in the dry run meeting minutes. Below is the link to refer to the dry run meeting minutes in eTMF

https://biodocumentum.bio.corpnet1.com/webtoppr/drl/objectId/090f45f688621990

Few tables were split as two separate tables in the updated TFL TOC by age category (as <6 years and ≥ 6 years), as the intensity score for the solicited symptoms are different for both the age categories.

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 analysis and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The mock tables referred under column named 'layout' can be found in 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 Group	Boostrix

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].

If some samples with anti-D concentrations < 0.1 IU/mL cannot be retested by VERO, VERO will be treated as left censored at 0.1 IU/mL and the Greenwoood formula for censored data will be used to estimate the percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥0.01 IU/mL by VERO and its associated CI .

The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.

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. 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.

11.2.3. Immunogenicity

- 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.

11.2.4. 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:

- Subjects who documented the absence of a solicited symptom will be considered not having that symptom.
- 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 without having recorded any daily measurement will be considered as having that symptom (at the lowest intensity).
- Intensity of the following solicited AEs will be assessed as described in Table 6 and below

Table 6 Intensity scales to be used by the parent(s)/LAR(s) for solicited symptoms during the solicited follow-up period

Toddler/Child (<6 years)		
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
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 ≥ 38.0°C. The preferred location for measuring temperature in this study will be the axilla.

Table 7 Intensity scales for solicited symptoms in adults and children of six years of age or more

Adult/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
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
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

***** Fever is defined as temperature ≥ 38.0°C. The preferred location for measuring temperature in this study will be the axilla.

The maximum intensity of local injection site redness/swelling for toddlers and children <6 years of age 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 local injection site redness/swelling for adults and children ≥6 years of age will be scored at GSK Biologicals as follows:

0	Absent
1	≤20 mm
2	>20 mm and ≤50 mm
3	>50 mm

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

0	*<38 ℃*
1	*≥38.0 ℃ to ≤39.0 ℃*
2	*>39.0 ℃ to ≤40.0 ℃*
3	*>40.0 ℃*

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**
Headache	10019211	Drowsiness
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	
Drowsiness	10013649	Drowsiness
Fever	10016558	Fever
Irritability/Fussiness	10022998	Irritability
Loss of appetite	10003028	Appetite lost
Pain at injection site	10022086	Injection site pain
Redness at injection site	10022098	Redness at injection site
Swelling at injection site	10053425	Swelling at injection site

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used.

The data display, title and footnote are for illustration purpose and will be adapted to the study specificity such as one group and one dose for the study.

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 (Total Vaccinated Cohort)

	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 (Total Vaccinated Cohort)

	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 (Total Vaccinated Cohort)

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 (Total Vaccinated Cohort)

		Age	VAC_1-SER_2	
Group		**Protocol**	**Protocol**	**Adapted**
		from 10 to 15 year	from 30 to 48 days	from 21 to 48 days
dTpaNew Group	N	335	329	329
	n	0	11	8
	%	0.0	3.3	2.4
	range	10 to 15	28 to 74	28 to 74
dTpaPre Group	N	336	329	329
	n	0	10	8
	%	0.0	3.0	2.4
	range	10 to 15	29 to 95	29 to 95

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
dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
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
VAC = vaccination
SER = Blood Sampling

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

		dTpaNew Group N = 335		dTpaPre Group N = 336		Total N = 671	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	11.9	-	11.9	-	11.9	-
	SD	1.59	-	1.61	-	1.60	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	10	-	10	-	10	-
	Maximum	15	-	15	-	15	-
Gender	Female	179	53.4	178	53.0	357	53.2
	Male	156	46.6	158	47.0	314	46.8
Geographic Ancestry	African Heritage / African American	1	0.3	1	0.3	2	0.3
	American Indian or Alaskan Native	146	43.6	149	44.3	295	44.0
	White - Arabic / North African Heritage	1	0.3	0	0.0	1	0.1
	White - Caucasian / European Heritage	9	2.7	12	3.6	21	3.1
	Other (Hispanic)	178	53.1	174	51.8	352	52.5

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = total number of subjects
n(%) = Number(percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Template 7 Summary of vital signs characteristics (Total Vaccinated Cohort)

		dTpaNew Group (N = 335)	dTpaPre Group (N = 336)	Total (N = 671)
Characteristics	**Parameters**	**Value**	**Value**	**Value**
Height (km)	Mean	152.6	151.5	152.1
	SD	10.48	10.44	10.47
	Median	152.0	151.5	152.0
	Minimum	112.0	126.0	112.0
	Maximum	189.0	187.0	189.0
	Unknown	0	0	0
Weight (kg)	Mean	49.7	48.8	49.2
	SD	13.23	13.61	13.42
	Median	47.0	47.1	47.0
	Minimum	28.0	19.4	19.4
	Maximum	99.0	110.0	110.0
	Unknown	0	0	0
BMI (kg/m²)	Mean	21.1	20.9	21.0
	SD	3.92	3.91	3.92
	Median	20.6	20.4	20.4
	Minimum	11.9	9.8	9.8
	Maximum	33.5	34.0	34.0
	Unknown	0	0	0

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Height (cm) = Height expressed in centimeters
Weight (kg) = Weight expressed in kilograms
BMI (kg/m^2) = Body Mass Index expressed in kilograms per meter square

Template 8 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 9 Seropositivity and seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies before and one month after the booster vaccination (ATP cohort for immunogenicity)

				≥ assay cut-off*				≥ 0.1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-diphtheria	dTpaNew Group	PRE	321	284	88.5	84.5	91.8	83	25.9	21.2	31.0	0.472	0.403	0.553
		POST	321	320	99.7	98.3	100	315	98.1	96.0	99.3	6.784	6.178	7.450
	dTpaPre Group	PRE	319	286	89.7	85.8	92.8	89	27.9	23.0	33.2	0.456	0.392	0.530
		POST	319	319	100	98.9	100	310	97.2	94.7	98.7	6.493	5.915	7.128
anti-tetanus	dTpaNew Group	PRE	321	311	96.9	94.3	98.5	151	47.0	41.5	52.7	0.956	0.835	1.095
		POST	321	321	100	98.9	100	321	100	98.9	100	18.937	17.313	20.713
	dTpaPre Group	PRE	319	314	98.4	96.4	99.5	143	44.8	39.3	50.5	0.899	0.789	1.026
		POST	319	319	100	98.9	100	319	100	98.9	100	18.515	16.851	20.342

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
Seroprotection=anti-diphtheria and anti-tetanus antibody concentration ≥0.1 IU/mL
*Assay cut-off is 0.057 IU/mL and 0.043 IU/mL for anti-diphtheria and anti-tetanus respectively
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n(%)=number(percentage) of subjects with antibody concentrations above the specified cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE=Pre-booster blood sampling time point
POST=Post-booster blood sampling time point

Template 10 Booster responses for anti-PT, anti-FHA and anti-PRN antibody concentration one month after the booster vaccination (ATP cohort for immunogenicity)

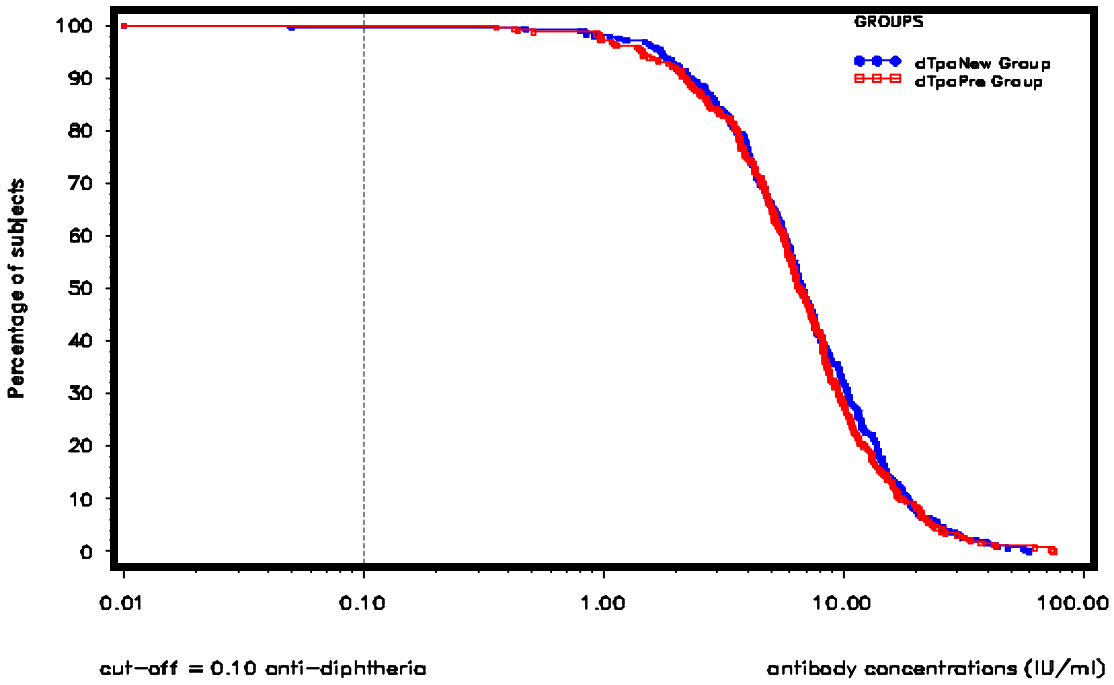
				Booster response			
						95% CI	
Antibody	**Group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
anti-PT	dTpaNew Group	S-	142	135	95.1	90.1	98.0
		S+ (< 4*assay cut-off)	104	103	99.0	94.8	100
		S+ (≥4*assay cut-off)	71	60	84.5	74.0	92.0
		Total	317	298	94.0	90.8	96.4
	dTpaPre Group	S-	143	131	91.6	85.8	95.6
		S+ (<4*assay cut-off)	114	112	98.2	93.8	99.8
		S+ (≥4*assay cut-off)	61	52	85.2	73.8	93.0
		Total	318	295	92.8	89.3	95.4
anti-FHA	dTpaNew Group	S-	6	6	100	54.1	100
		S+ (<4*assay cut-off)	57	57	100	93.7	100
		S+ (≥4*assay cut-off)	251	242	96.4	93.3	98.3
		Total	314	305	97.1	94.6	98.7
	dTpaPre Group	S-	5	5	100	47.8	100
		S+ (<4*assay cut-off)	55	55	100	93.5	100
		S+ (≥4*assay cut-off)	255	244	95.7	92.4	97.8
		Total	315	304	96.5	93.8	98.2
anti-PRN	dTpaNew Group	S-	52	50	96.2	86.8	99.5
		S+ (<4*assay cut-off)	152	151	99.3	96.4	100
		S+ (≥4*assay cut-off)	117	114	97.4	92.7	99.5
		Total	321	315	98.1	96.0	99.3
	dTpaPre Group	S-	47	47	100	92.5	100
		S+ (<4*assay cut-off)	159	159	100	97.7	100
		S+ (≥4*assay cut-off)	112	111	99.1	95.1	100
		Total	318	317	99.7	98.3	100

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
S- = Initially seronegative subjects prior to vaccination
S+ = Initially seropositive subjects prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
S- = seronegative subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
S+ = seropositive (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
Booster response to PT, FHA and PRN antigens is defined as:

- initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
- initially seropositive subjects with anti-body concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination
- initially seropositive subjects with anti-body concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination

Assay cut-off is 2.693 IU/mL, 2.046 IU/mL and 2.187 IU/mL for anti-PT, FHA and PRN respectively
N = number of subjects with both pre- and post-vaccination results available
n(%) = number(percentage) of subjects with a booster response
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 11 Reverse cumulative curve for anti-diphtheria antibody concentration one month after the booster vaccination (ATP cohort for immunogenicity)



dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation

Template 12 Seroprotection rate for anti-Diphtheria antibody concentration by ELISA and VERO NEUTRALISATION (ATP cohort)

			ELISA concentrations below the 0.1 IU/ml		Neutra concentrations below the 0.01 IU/ml among subjects with ELISA concentrations below the 0.1 IU/ml		Neutra concentrations below the 0.01 IU/ml among subjects with ELISA results		Estimated proportion of protected subjects (SP) and its 95% CI		
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
(each group)	Pre										
	post										

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
N = number of subjects tested by ELISA
N' = number of subjects with ELISA concentrations below the 0.1 IU/ml who were tested by Vero
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ml for ELISA and 0.01 IU/ml for VERO) n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-Diphtheria
Overall = based on both the ELISA and the Vero-cell neutralisation testing
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Pre= blood sampling, at Month 0 before vaccination
post= blood sampling, one motnh after vaccination
SP= proportion of subjects with either ELISA concentrations above 0.1 IU/ml or Neutra concentration above 0.01 IU/mL

Template 13 Compliance in returning symptom information (Total Vaccinated Cohort)

Group	**Number of doses**	**Doses NOT according to protocol**	**Number of general SS**	**Compliance % general SS**	**Number of local SS**	**Compliance % local SS**
dTpaNew Group	335	0	330	98.5	330	98.5
dTpaPre Group	336	1	329	97.9	329	97.9

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Template 14 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**
dTpaNew Group	335	264	78.8	74.0	83.1	335	134	40.0	34.7	45.5	335	250	74.6	69.6	79.2
dTpaPre Group	336	279	83.0	78.6	86.9	336	151	44.9	39.5	50.4	336	264	78.6	73.8	82.8

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the administered dose
n(%)= number(percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 15 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) period after vaccination following each dose and overall (Total Vaccinated Cohort)

		dTpaNew Group					dTpaPre Group				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	330	237	71.8	66.6	76.6	329	248	75.4	70.4	79.9
	Grade 3	330	24	7.3	4.7	10.6	329	20	6.1	3.8	9.2
	Medical advice	330	0	0.0	0.0	1.1	329	0	0.0	0.0	1.1
Redness (mm)	All	330	113	34.2	29.1	39.6	329	94	28.6	23.8	33.8
	Grade 3	330	4	1.2	0.3	3.1	329	1	0.3	0.0	1.7
	Medical advice	330	0	0.0	0.0	1.1	329	0	0.0	0.0	1.1
Swelling (mm)	All	330	98	29.7	24.8	34.9	329	90	27.4	22.6	32.5
	Grade 3	330	6	1.8	0.7	3.9	329	5	1.5	0.5	3.5
	Medical advice	330	0	0.0	0.0	1.1	329	0	0.0	0.0	1.1

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the 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 16 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

		dTpaNew Group					dTpaPre Group				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All	330	83	25.2	20.6	30.2	329	86	26.1	21.5	31.2
	Grade 3	330	7	2.1	0.9	4.3	329	4	1.2	0.3	3.1
	Related	330	77	23.3	18.9	28.3	329	83	25.2	20.6	30.3
	Medical advice	330	1	0.3	0.0	1.7	329	1	0.3	0.0	1.7
Gastrointestinal	All	330	32	9.7	6.7	13.4	329	42	12.8	9.4	16.9
	Grade 3	330	3	0.9	0.2	2.6	329	3	0.9	0.2	2.6
	Related	330	29	8.8	6.0	12.4	329	40	12.2	8.8	16.2
	Medical advice	330	2	0.6	0.1	2.2	329	1	0.3	0.0	1.7
Headache	All	330	88	26.7	22.0	31.8	329	108	32.8	27.8	38.2
	Grade 3	330	5	1.5	0.5	3.5	329	3	0.9	0.2	2.6
	Related	330	80	24.2	19.7	29.2	329	103	31.3	26.3	36.6
	Medical advice	330	2	0.6	0.1	2.2	329	1	0.3	0.0	1.7
Temperature/(Axillary) (°C)	All	330	9	2.7	1.3	5.1	329	6	1.8	0.7	3.9
	≥37.5	330	9	2.7	1.3	5.1	329	6	1.8	0.7	3.9
	>38.0	330	5	1.5	0.5	3.5	329	1	0.3	0.0	1.7
	>38.5	330	3	0.9	0.2	2.6	329	1	0.3	0.0	1.7
	>39.0	330	2	0.6	0.1	2.2	329	0	0.0	0.0	1.1
	Related	330	7	2.1	0.9	4.3	329	6	1.8	0.7	3.9
	Medical advice	330	2	0.6	0.1	2.2	329	0	0.0	0.0	1.1

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the 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
Related = Symptoms which is assessed by the investigator as related to vaccination
Grade3*Related = Grade 3 symptom which is assessed by the investigator as related to vaccination
Grade 3 For Headache: Headache that prevented normal activity
For Fatigue: Fatigue that prevented normal activity
For Gastrointestinal symptoms: Gastrointestinal symptoms that prevented normal activity
For Fever: >39.0 °C

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 (Total Vaccinated Cohort)

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

Primary System Organ Class (CODE)	Preferred Term (CODE)	HRV LIQ N = 298				HRV LIQ N = 302				HRV LIQ N = 300			
				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pneumonia (10035664)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Respiratory tract infection (10062352)	3	1.0	0.2	2.9	2	0.7	0.1	2.4	0	0.0	0.0	1.2
	Respiratory tract infection viral (10062106)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rhinitis (10039083)	2	0.7	0.1	2.4	1	0.3	0.0	1.8	3	1.0	0.2	2.9
	Upper respiratory tract infection (10046306)	2	0.7	0.1	2.4	5	1.7	0.5	3.8	7	2.3	0.9	4.7
	Varicella (10046980)	0	0.0	0.0	1.2	1	0.3	0.0	1.8	2	0.7	0.1	2.4
Psychiatric disorders (10037175)	Crying (10011469)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	6	2.0	0.7	4.3
	Nasal congestion (10028735)	1	0.3	0.0	1.9	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	Rales (10037833)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.3	0.0	1.9	1	0.3	0.0	1.8	0	0.0	0.0	1.2
	Eczema (10014184)	0	0.0	0.0	1.2	0	0.0	0.0	1.2	1	0.3	0.0	1.8
	Rash (10037844)	2	0.7	0.1	2.4	0	0.0	0.0	1.2	0	0.0	0.0	1.2

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

Template 18 Number (%) of subjects with serious adverse events from first study vaccination up to Visit 3 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 19 Subjects with Serious Adverse Events reported up to Visit 2 (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	Causality	Outcome
PPD	PPD	12	M	Kawasaki's disease	Kawasaki's disease	Infections and infestations	HO	1	12	29	N	Recovered/resolved
PPD	PPD	18	M	Influenza-b	Influenza	Infections and infestations	HO	2	2	5	N	Recovered/resolved
PPD	PPD	17	M	Acute gastroenteritis	Gastroenteritis	Infections and infestations	HO	2	9	5	N	Recovered/resolved
PPD	PPD	17	F	Infantile spasms	Infantile spasms	Nervous system disorders	HO	2	2	51	N	Recovered/resolved with sequelae
PPD	PPD	21	M	Rs-virus bronchiolitis	Respiratory syncytial virus bronchiolitis	Infections and infestations	HO	2	30	16	N	Recovered/resolved
PPD	PPD	13	M	Gastroenteritis	Gastroenteritis	Infections and infestations	HO	1	25	6	N	Recovered/resolved
PPD	PPD	22	M	Pneumonia	Pneumonia	Infections and infestations	HO	2	32	13	N	Recovered/resolved
		23		Middle ear infection	Otitis media	Infections and infestations	HO	2	37	8	N	Recovered/resolved
PPD	PPD	14	F	Secretory otitis media	Otitis media	Infections and infestations	HO	1	7	25	N	Recovered/resolved
PPD	PPD	20	M	Viral pneumonia	Pneumonia viral	Infections and infestations	HO	2	13	23	N	Recovered/resolved
PPD	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

Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
PPD	PPD	14	M	Bronchitis acuta	Bronchitis	Infections and infestations	HO	1	23	12	N	Recovered/resolved
PPD	PPD	19	M	Bronchiolitis acuta	Bronchiolitis	Infections and infestations	HO	2	26	7	N	Recovered/resolved
PPD	PPD	19	F	Laryngitis acuta	Laryngitis	Infections and infestations	HO	2	7	4	N	Recovered/resolved
PPD	PPD	18	F	Laryngitis	Laryngitis	Infections and infestations	HO	2	7	4	N	Recovered/resolved
PPD	PPD	14	F	Gastroenteritis	Gastroenteritis	Infections and infestations	HO	1	22	7	N	Recovered/resolved

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

Template 20 Number and percentage of subjects who started at least one concomitant medication from Day 0 to Day 7 (Total Vaccinated Cohort)

	dTpaNew Group					dTpaPre Group				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Any	335	41	12.2	8.9	16.2	336	43	12.8	9.4	16.8
Any antipyretic	335	37	11.0	7.9	14.9	336	41	12.2	8.9	16.2
Prophylactic antipyretic	335	2	0.6	0.1	2.1	336	2	0.6	0.1	2.1

dTpaNew Group = Subjects who received *Boostrix* in new syringe presentation
dTpaPre Group = Subjects who received *Boostrix* in previous syringe presentation
N = number of subjects with the administered dose
n(%)= number(percentage) of subjects who started to take the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 21 Solicited and Unsolicited symptoms experienced by subjects classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period - 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 22 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 23 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 24 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 25 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 26 Percentage of subjects with large injection site reaction during the 4-day (Days 0-3) period after Boostrix (Total Vaccinated Cohort)

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 = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 27 GMCs fold increase for anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies one month after the booster vaccination by study (Per protocol cohort for analysis of immunogenicity)

							GMC ratio			
									95% CI	
Antibody	Sub-grp	N	Time point description	GMC	Time point description	GMC	Ratio order	Value	LL	UL
Anti-Diphtheria (IU/mL)			POST		PRE		POST / PRE			
…										

GMC = geometric mean antibody concentration
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
PRE = blood sample taken before the booster vaccination
POST = blood sample taken one month after the booster vaccination