GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of a booster dose of Infanrix hexa™ in healthy infants born to mothers vaccinated with Boostrix™ during pregnancy or immediately post-delivery.
eTrack study number and Abbreviated Title	201334 [DTPA (BOOSTRIX)-049 BST: 048]
Scope:	All data pertaining to the above study and also the previous studies DTPA (BOOSTRIX)-047 and DTPA (BOOSTRIX)-048 PRI.
Date of Statistical Analysis Plan	Final: 22-MAR-2019
Co-ordinating author:	PPD
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer) PPD (Stat Peer Reviewer) PPD (Regulatory Affairs) PPD (Safety Scientist) PPD (Safety Physician) PPD (Safety Physician) PPD (Safety Scientist) PPD (Public disclosure representative)
Approved by:	PPD (Clinical and Epidemiology Project Lead) PPD (Lead statistician) PPD (Statistician) PPD (Lead statistical analyst) PPD (Lead Scientific writer) PPD (Scientific writer) PPD (Clinical Research and Development Lead)

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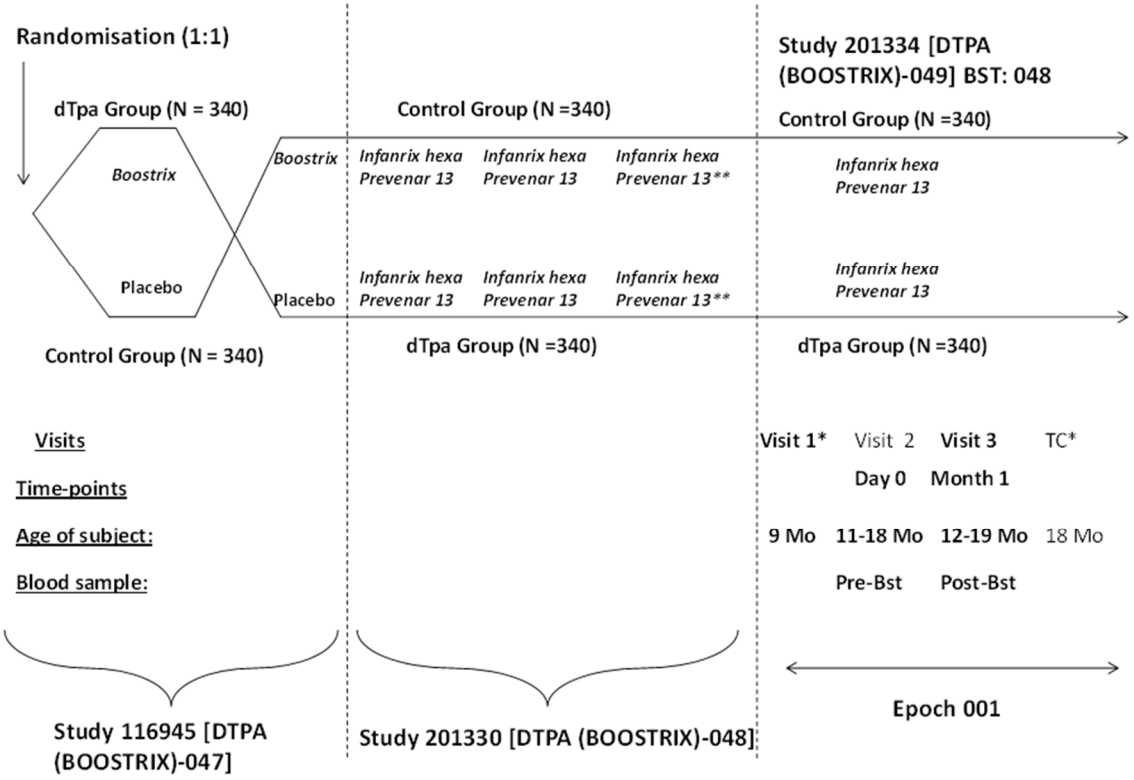
LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of Variance
ASQ-3	Ages & Stages Questionnaires, third edition
CA	Congenital anomaly
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EL.U/mL	ELISA unit per milliliter
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
eTMF	Electronic Trial Master File
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
LLOQ	Lower limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
ToC	Table of Content
UL	Upper Limit of the confidence interval
WBR	Web-based Randomisation

1. DOCUMENT HISTORY

Date	Description	Protocol Version
22 MAR 2019	First version	Final: 12 DEC 2016

2. STUDY DESIGN OBJECTIVES/ENDPOINTS



N: Maximum Number of subjects planned to be enrolled; Mo: Age in Months
*The neurodevelopmental status will be recorded when the subject is 9 months and 18 months of age. It is encouraged that subjects who are getting vaccinated at 18 months of age at Visit 2 or coming for Visit 3, complete their ASQ-3 during their visit to the study centre. In case subjects complete Visit 3 before 18 months of age, the study staff will contact the parents/LAR(s) via phone and conduct an interview to complete the child's ASQ-3 at 18 months of age. For Czech Republic, the phone call at 18 months may be replaced by a clinic visit if deemed preferable by the study team.
** Subjects have received either 2 or 3 doses of Infanrix hexa and Prevnar during the course of the study DTPA (Boostrix)-048, depending on the national/ local routine immunization schedule.
Refer to Section 5.6.2.13 of the protocol for further details.
Pre-Bst: Blood sample to be collected before the booster dose.
Post-Bst: Blood sample to be collected one month after the booster dose.

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

- Experimental design: Phase IV, open-label, non-randomised, multi-centric, multi-country study with two parallel groups.

- Duration of the study: The intended duration of the study, is approximately 9 to 10 months, per subject.
  - Epoch 001: Booster phase starting at Visit 1 (9 months of age) and ending at telephone contact or at Visit 3 (18 or 19 months of age), depending on the time of vaccination. End of Study (EoS): Last testing results released of samples collected at Visit 3.
- Study groups: The study groups and epoch foreseen in the study are presented in Table 1.
  - dTpa Group: This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] i.e., mothers who received a single dose of *Boostrix* during pregnancy and a dose of placebo immediately post-delivery and infants who received full primary vaccination course as per protocol requirement in the study 201330 [DTPA (BOOSTRIX)-048 PRI]. All subjects in this group will receive a booster dose of *Infanrix hexa* co-administered with Prevenar 13 according to the routine national/ local immunization schedule or as specified in the SPM.
  - Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047] i.e., mothers who received a single dose of placebo during pregnancy and a dose of *Boostrix* immediately post-delivery and infants who received full primary vaccination course as per protocol requirement in the study 201330 [DTPA (BOOSTRIX)-048 PRI]. All subjects in this group will receive a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/ local immunization schedule or as specified in the SPM.

Table 1 Study groups and epoch foreseen in the study

Study groups	Number of subjects*	Age (Min/Max)**	Epoch
			Epoch 001
dTpa Group	340	11 months-19 months	x
Control Group	340	11 months-19 months	x

*Maximum number of subjects
**Age at the time of vaccination depending on routine national/ local immunization schedule or as specified in the SPM

The study groups and treatment foreseen in the study is presented in Table 2.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		dTpa Group	Control Group
Infanrix hexa	DTPa-HBV-IPV	x	x
	Hib	x	x
Prevenar 13	Prevenar 13	x	x

- Control: uncontrolled (No active control or placebo. All subjects will receive the same vaccine)
- Vaccination schedule: All subjects will receive a booster dose of *Infanrix hexa* co-administered with *Prevenar 13* between 11-18 months of age according to the routine national/ local immunization schedule or as specified in the SPM.
- Treatment allocation: Non-randomised. All subjects will receive a booster dose of *Infanrix hexa* co-administered with *Prevenar 13*.
- Blinding: Open-label. Note: The study personnel operating with the GSK Biologicals' central Randomisation System on Internet (SBIR) and the site staff will remain blinded towards the treatment allocation of the mother in study 116945 [DTPA (BOOSTRIX)-047].

The blinding of study epoch is presented in Table 3.

Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	open

- Sampling schedule: Blood samples will be drawn from all subjects at the following time points:
  - Pre-Bst: Before the booster dose administration, a volume of approximately 5 mL of whole blood (to provide approximately 1.7 mL of serum) will be collected.
  - Post-Bst: One month after the booster dose, approximately 5 mL of whole blood (to provide approximately 1.7 mL of serum) will be collected.
- Type of study: extension of other protocol(s) 116945 [DTPA (BOOSTRIX)-047] and 201330 [DTPA (BOOSTRIX)-048 PRI].
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: An independent data monitoring committee (IDMC) (including paediatricians and a statistician) will be put in place to oversee the safety aspects including neurodevelopmental status of infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery in the clinical study i.e., each SAE/incidence of grade 3 local and general solicited AEs, unsolicited AEs will be reviewed by this committee as per approved IDMC charter.

3. OBJECTIVES

3.1. Primary objective

- To assess the immunological response to *Infanrix hexa* in terms of seroprotection status for diphtheria, tetanus, hepatitis B, poliovirus and Hib antigens, and in terms of booster response for the pertussis antigens, one month after the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.

Refer to Section 3.3 for the definition of the primary endpoint.

3.2. Secondary objectives

- To assess the persistence of antibodies to all vaccine antigens before the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.
- To assess the immunological response to *Infanrix hexa* and *Prevenar 13* in terms of antibody concentrations or titres against all antigens, one month after the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.
- To assess the immunological response to *Infanrix hexa* in terms of seropositivity rates against pertussis antigens, one month after the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.
- To assess the safety and reactogenicity of *Infanrix hexa* and *Prevenar 13* in terms of solicited and unsolicited symptoms and serious adverse events (SAEs).
- To assess the neurodevelopmental status of infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery, at 9 and 18 months of age.

3.3. Primary endpoint

- Immunogenicity with respect to components of *Infanrix hexa.*
  - Anti-diphtheria, anti-tetanus, anti-HBs, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3 and anti-polyribosyl-ribitol phosphate (anti-PRP) seroprotection status, one month after the booster dose.
  - Booster response to PT, FHA and PRN antigens, one month after the booster dose.

Refer to section 5.3.2 for the definition of the booster response

3.4. Secondary endpoints

- Immunogenicity with respect to components of *Infanrix hexa* and *Prevenar 13*.

Before the booster dose

- Anti-diphtheria, anti-tetanus, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3, anti-HBs and anti-PRP seroprotection status.
- Anti-PT, anti-FHA and anti-PRN and anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) seropositivity rates.
- Anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3, anti-HBs and anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) and anti-PRP antibody concentrations or titres.

One month after the booster dose

- Anti-diphtheria, anti-tetanus, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3, anti-HBs, anti-PRP, anti-PT, anti-FHA, anti-PRN and anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations or titres.
- Anti-PT, anti-FHA, anti-PRN antibody seropositivity rates.

- Solicited local and general symptoms.
  - Occurrence of solicited local/general symptoms during the 4-day (Day 0-Day 3) follow-up period after booster vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited symptoms during the 31-day (Day 0-Day 30) follow-up period after booster vaccination.
- Serious adverse events.
  - Occurrence of reported SAEs from booster dose up to study end.
- Neurodevelopmental status will be assessed at 9 and 18 months of age adjusted for prematurity.
  - Proportion of infants with an ASQ-3 score in the black zone in any domain.
  - Proportion of infants with an ASQ-3 score in the black zone for gross motor skills.
  - Proportion of infants with an ASQ-3 score in the black zone for fine motor skills.
  - Proportion of infants with an ASQ-3 score in the black zone for communication.
  - Proportion of infants with an ASQ-3 score in the black zone for problem solving skills.
  - Proportion of infants with an ASQ-3 score in the black zone for personal-social skills.
  - Proportion of infants referred for formal neurodevelopmental evaluation using BSID-III.

– Proportion of infants with at least one of the indicators of neurodevelopmental impairment using BSID-III.

4. ANALYSIS SETS

4.1. Definition

Four cohorts are defined for the purpose of the analysis:

- Total enrolled cohort
- Total Vaccinated cohort (TVC).
- ATP cohort for analysis of safety
- ATP cohort for analysis of immunogenicity

4.1.1. Total enrolled cohort

The Total enrolled cohort will include all enrolled subjects in the study.

4.1.2. Total vaccinated cohort

The TVC will include all vaccinated subjects for whom data are available.

A safety analysis based on the TVC will include all subjects with booster vaccine administration documented.

- An immunogenicity analysis based on the TVC will include vaccinated subjects for whom data concerning immunogenicity endpoint measures are available.

4.1.3. According-to-protocol cohort for analysis of safety

The ATP cohort for analysis of safety will include all subjects from the TVC who complied with the vaccine administration:

- who have received all vaccine dose*s* in the primary study 201330 [DTPA (BOOSTRIX)-048 PRI].
- who have received the booster dose of study vaccines in the current study.
- for whom administration route and site of study vaccines is known and according to the protocol.
- who have not received a vaccine not specified or forbidden in the protocol.

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

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who meet all eligibility criteria.
- Who received all doses of vaccine in the primary study 201330 [DTPA (BOOSTRIX)-048 PRI].
- Who comply with the procedures and intervals defined in the protocol (refer to Table 5 of the protocol).
- Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 6.7.2 of the protocol).
- Who did not receive a product leading to elimination from an ATP analysis as listed in Section 6.7.2 of the protocol,
- Who did not present with a medical condition leading to elimination from an ATP analysis as listed in Section 6.8 of the protocol,
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination.
- The interval between the vaccination visit and post-booster blood sampling, considered for inclusion of a subject will be 21–48 days.

4.1.5. Adapted ATP cohort

When presenting different time points, the Adapted ATP cohort will be used to denote that for each time point, the corresponding ATP cohort for immunogenicity has been used.

More specifically,

- The analyses on the pre and post booster dose time points in mothers, and the cord blood sample will be based on the ATP cohort for immunogenicity in study 116945 (Boostrix-047)
- The analysis on the pre and post primary time points in infants will be based on the ATP cohort for immunogenicity in study 201330 (Boostrix-048).
- The analysis on the pre and post booster time points in infants will be based on the ATP cohort for immunogenicity in study 201334 (Boostrix-049).

4.2. 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 set.

4.2.1. Elimination from Total Vaccinated cohort (TVC)

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

4.2.2. Elimination from ATP cohort for safety

4.2.2.1. Excluded subjects

All eliminations from the study 201330 [DTPA (BOOSTRIX)-048 PRI] will be applicable for this follow up study except for the visit specific elimination codes (2090, 2100 and 2120).

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

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set (Safety, immunogenicity)
800	Fraudulent data. Also inherited from the 048 study	all	all
900	Invalid informed consent or fraudulent data Also inherited from the 048 study.	all	all
1030	Study vaccine not administered at all. Also inherited from the 048 study.	Visit 2	Safety, immunology
1040	Administration of concomitant vaccine(s) forbidden in the protocol • Concurrently participating in another clinical study, within three months prior to the booster vaccine dose and at any time during the present booster study, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device). • A vaccine not foreseen by the study protocol administered during the period starting from 30 days before the booster dose of study vaccine and ending 30 days after*, with the exception of inactivated influenza vaccine and other vaccines given as a part of the national/regional immunisation schedule, that are allowed at any time during 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 SPC or Product Information (PI) and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.	Visit 2	Safety, immunology

	Also inherited from the 048 study.		
1050	Randomisation failure (subject who received a vaccine not compatible with randomization) Also inherited from the 048 study.	Carried forward from previous study	Safety, immunology
1060	Randomisation code broken at the investigator site OR at GSK Safety department. This code is inherited from the mother. Also inherited from the 048 study.	Visit 2	Safety, immunology
1070	Vaccination not according to protocol Site or route of study vaccine administration wrong or unknown. Also inherited from the 048 study.	Visit 2	Safety, immunology
1080	Vaccine temperature deviation (vaccine administration not as per protocol) => *Infanrix hexa* vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation. Also inherited from the 048 study.	Visit 2	Safety, immunology
1090	Expired vaccine administered (vaccine administration not as per protocol)=> Subjects who received an expired Infanrix hexa. Also inherited from the 048 study.	Visit 2	Safety, immunology

4.2.3. Elimination from ATP cohort for immunogenicity

4.2.3.1. Excluded subjects

All eliminations from the study 201330 [DTPA (BOOSTRIX)-048 PRI] will be applicable for this follow up study except for the visit specific elimination codes (2090, 2100 and 2120).

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

A subject will be excluded from the ATP cohort for immunogenicity when he/she is excluded from the ATP cohort for safety (see Section 4.1.3).

The following additional codes will be used:

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set (Safety, immunogenicity)
2010	Protocol violation (inclusion/exclusion criteria not fulfilled) • Window from DOB to vaccination is 11-18(+30 days) months of age according to the routine national/ local immunization schedule or as specified in the SPM • Healthy subjects as established by medical history and clinical examination before entering into the study. • Previous booster vaccination against Hib, diphtheria, tetanus, pertussis, pneumococcus, hepatitis B and/or poliovirus since the conclusion visit of study 201330 [DTPA (BOOSTRIX)-048 PRI]. • Subjects born to mothers who were vaccinated in 116945 [DTPA (BOOSTRIX)-047] study and having completed their primary vaccination series as per protocol requirement in study 201330 [DTPA (BOOSTRIX)-048 PRI]. Also inherited from the 048 study.	Visit 1/2	Immunogenicity
2040	Administration of any medication forbidden by the protocol • Administration of immunoglobulins and/or any blood products during the period within three months before the booster dose of study vaccines or planned administration during the study period. Also inherited from the 048 study.	Visit 2/3	Immunogenicity
2050	Underlying medical condition forbidden by the protocol => Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (e.g. any confirmed or suspected immunosuppressive or immunodeficient condition) or are confirmed to have an alteration of their initial immune status. Also inherited from the 048 study.	Visit 2/3	Immunogenicity
2080	Subjects did not comply with vaccination schedule Inherited from the 048 study.	Carried forward from previous study	Immunogenicity
2090	Subjects did not comply with blood sample schedule(date of blood sampling not corresponding to adapted protocol intervals or unknown blood sample date) => 21-48 days from vaccination (Visit 2)	Visit 3	Immunogenicity
2100	Serological results not available for antigens POST vaccination (including lost samples, blood sample not done, unable to test, absence of parallelism) => no immunogenicity results available at visit 3.	Visit 3	Immunogenicity

2120	Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results, wrong sample labelling)	Visit 3	Immunogenicity

5. STATISTICAL ANALYSES

Note that standard data derivation rules and stat methods are described in "business rules document" and will not be repeated below. The study specific data derivation rules and stat methods will be described in section 9.

5.1. Demography

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

Demographic characteristics (age in months, race, length [cm], weight [kg], head circumference [cm]), cohort description and withdrawal status will be summarised by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as race, country or primary vaccination schedule (2 dose vs. 3 dose in study 048);
- Mean, median and standard error will be provided for continuous data such as age.

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

5.1.2. Additional considerations

Gender, country, maternal age group (18-24Y, 25-34Y and 35-45Y) and gestational age at dose 1 in the primary study (27-32W, 33-36W) will also be summarised by group using above mentioned descriptive statistics.

All demography summaries will be generated for the TVC. The summary of age, length[cm], Weight [kg], head circumference, gender will also be provided for the ATP cohort for immunogenicity.

Number and reason for elimination from ATP cohorts will be tabulated by group.

Quartile 1 and quartile 3 will be provided for continuous data such as age in months, race, length [cm], weight [kg], head circumference [cm], body mass index in [kg/m^2].

5.2. Exposure

NA.

5.2.1. Analysis of exposure planned in the protocol

NA.

5.2.2. Additional considerations

The doses administered will be summarized by vaccine.

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If in any vaccine group, the percentage of enrolled subjects excluded from this ATP cohort is more than 5%, a second analysis based on the TVC will be performed to complement the ATP analysis. All analyses will be descriptive.

For each group, at each time point that a blood sample result is available:

- Seropositivity rates against PT, FHA and PRN antigens and pneumococcal antigens (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) with exact 95% CI [Clopper, 1934] will be calculated.
- Seroprotection rates against diphtheria toxoid, tetanus toxoid, HBs, PRP antigen and poliovirus types 1, 2, 3 antigens (with exact 95% CI [Clopper, 1934]) will be calculated.
- Percentage of subjects with anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations, depending on the GSK laboratory or WHO reference laboratory assay cut-offs, will be calculated along with its exact 95% CI [Clopper, 1934].
- Percentage of subjects with anti-D and anti-T antibody concentrations ≥ 1.0 IU/ml will be calculated along with its exact 95% CI [Clopper, 1934].
- Percentage of subjects with anti-PRP antibody concentrations ≥ 1.0 µg/ml and anti-HBs antibody concentrations ≥ 100 mIU/mL will be calculated along with its exact 95% CI [Clopper, 1934].
- GMC/GMT with 95% CI will be tabulated for antibodies against each antigen.
- The booster response rates to PT, FHA and PRN (with exact 95% CI) one month after the booster dose will be calculated.

The above summaries will be provided by country or primary vaccination schedule for countries involving more than 50 subjects.

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

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.

5.3.2. Additional considerations

Considering that RCC are available and the percentage of subjects with titres/concentration above key thresholds are available, the distribution of antibody concentrations or titres of each antigen will not be tabulated.

Following the re-validation of the pertussis assays, the booster response to the 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

Percentage of subjects with anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) above the assay cut-offs, will be calculated along with its exact 95% CI [Clopper, 1934].

In addition to the percentage of seroprotected or seropositive subjects, the percentage of subjects above the assay cut off and percentage of subjects above the following cut-off will be summarized

- Anti-PRP antibody concentrations ≥ 1.0 µg/mL.
- Anti-diphtheria antibody concentrations ≥ 1.0 IU/mL.
- Anti-tetanus antibody concentrations ≥ 1.0 IU/mL.
- Anti-HBs antibody concentrations ≥ 100 mIU/mL.
- Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) ≥ 0.35 µg/mL.

In addition, subgroups analysis according to gestational age (27-32 weeks and 33-36 weeks) and age of the mother at dose 1 in the primary study (18-24 year, 25-34 year and 35-45 year) will be performed.

The sub-group analyses will be limited to descriptive tables of GMT/GMC and the percentage of subjects with titres/concentration above key thresholds for ATP cohort of immunogenicity.

In light of the number of subjects enrolled in each country, the analysis by country will be replaced with analysis by schedule of the primary vaccination (2 doses ie 2,4 months combined with 3,5 months versus 3 doses i.e. 2,3,4 months combined with 2,4,6 months).

The immunogenicity analysis for the pertussis antigens will be generated on the adapted ATP cohort taking in to account all the time points from the study Boostrix 047 up to the current study.

The kinetics of the observed GMCs of the pertussis antigens across all the time points will be plotted in an evolution graph with confidence interval.

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

The primary analysis will be based on the TVC. If more than 5% of enrolled subjects are excluded from the ATP cohort for analysis of safety, then a second analysis based on this ATP cohort will be performed to complement the TVC analysis. All analyses will be descriptive.

- 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 0-Day 3) solicited follow-up period will be tabulated with exact 95% CI [Clopper, 1934]. The same calculations will be done for symptoms (solicited or unsolicited) rated as grade 3 in intensity, for symptoms (solicited or unsolicited) leading to medical advice and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.
- The incidence of local AEs (solicited and unsolicited) will be calculated at each injection site as well as overall (all sites considered) for each group.
- The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 0-Day 3) solicited follow-up period will be tabulated after the vaccine dose, with exact 95% CI [Clopper, 1934]. 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.
- All computations mentioned above will be done for Grade ≥2 (solicited symptoms only) and grade 3 symptoms, for symptoms considered related to vaccination (general symptoms only), for grade 3 symptoms considered related to vaccination (general symptoms only) and for symptoms that resulted in a medically-attended visit.
- Occurrence of fever and related fever will be reported per 0.5°C cumulative temperature increments as well as the occurrence of grade 3 fever (> 39.0°C axillary temperature) with causal relationship to vaccination.

- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day (Day 0- Day 30) follow-up period after any dose with its exact 95% CI [Clopper, 1934] will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and AEs/SAEs leading to withdrawal from the study.
- The percentage of subjects who receive concomitant medication and antipyretic medication during the 4-day (Day 0- Day 3) follow-up period and during the entire study period will be tabulated (with exact 95% CI [Clopper, 1934]) after the booster dose.
- Any large injection site reaction (defined as any local swelling with diameter > 50 mm and/or any noticeable diffuse injection site swelling (diameter not measurable) and/or any noticeable increased circumference of the injected limb) reported within 4 days (Day 0-Day 3) following the booster dose will be described in detail.
- Subjects who experience at least one SAE from booster vaccination up to study end will be described in detail.
- Subjects who report at least one SAE after the end of primary study 201330 [DTPA (BOOSTRIX)-048 PRI] and before 201334 [DTPA (BOOSTRIX)-049 BST: 048] study will be described in detail.
- Withdrawal due to AEs and SAEs following vaccinations will be described in detail.
- For the subjects who withdraw from the study after Visit 1 (after completion of ASQ-3 questionnaire but have not received booster vaccination), the analysis will be performed on the Total enrolled cohort.
- Neurodevelopmental status of the subjects will be assessed depending on the ASQ-3 score. The proportion of subjects in the black zone for any domain, for gross motor skills, fine motor skills, communication, problem solving skills and personal-social skills will be tabulated. The proportion of infants referred for formal neurodevelopmental evaluation using BSID-III and those with at least one indicators of neurodevelopmental impairment using BSID-III will also be tabulated.

Handling of missing data:

- For a given subject and the analysis of solicited AEs, four days post-vaccination (Day 0-Day 3), missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited AEs based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e., symptom screen completed).
- For a given subject, missing neurodevelopmental status will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements

- 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, whose parent(s)/LAR(s) 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 and unsolicited AEs, all vaccinated subjects will be considered. Subjects, whose parent(s)/LAR(s) do not report the event or the concomitant medication, will be considered as subjects without the event or the concomitant medication, respectively.

5.4.2. Additional considerations

- The AEs/SAEs leading to withdrawal from the study will be generated as a listing instead of a table.
- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day (Day 0- Day 30) follow-up period after the booster dose with its exact 95% CI [Clopper, 1934] will be tabulated by group, and by preferred term.
- Subjects who report at least one SAE after the end of primary study 201330 [DTPA (BOOSTRIX)-048 PRI] and before the booster vaccination in 201334 [DTPA (BOOSTRIX)-049 BST: 048] study will be described in detail.
- The percentage of subjects with congenital anomaly reported across the three studies (047, 048 and 049) with its exact 95% CI [Clopper, 1934] will be tabulated by group, and by preferred term. The details of this analysis are detailed in section 9.
- The neurodevelopmental status of infants will be tabulated at both month 9 and 18.

5.4.2.1. Combined Solicited and Unsolicited Adverse Events

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA as per the following codes.

Solicited symptom	Lower level term code	Corresponding Lower level term decode
PA	10022086	Injection site pain
RE	10022098	Redness at injection site
SW	10053425	Swelling at injection site
TE	10016558	Temperature/Fever
FU	10022998	Irritability/Fussiness
DR	10013649	Drowsiness
LO	10003028	Loss of appetite
LS	10060708	Large injection swelling

6. ANALYSIS INTERPRETATION

All analyses are descriptive.

7. 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.

7.1. Sequence of analyses

The final analyses of all data will be conducted when all data are available. This analysis will include the final analysis of immunogenicity and the final analysis of solicited and unsolicited symptoms and SAEs. A clinical study report containing all data will be written and made available to the investigators.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal, 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

7.2. Statistical considerations for interim analyses

No interim analysis is planned for this study.

8. CHANGES FROM PLANNED ANALYSES

- During the course of the study, the assays used to measure the anti-D, anti-T, anti-PT, anti-FHA and anti-PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISA's for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISA's in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA's used in the study have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/mL for anti-D, 0.043 IU/mL for anti-T, 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN. An agreement between the old and new ELISAs was shown with regards to the two thresholds of clinical relevance for the DI/TE response (0.1 IU/mL and 1.0 IU/mL) and therefore the clinical endpoints and anti-D and anti-T are unchanged. In the absence of a correlate of protection for the B. pertussis antigens, the pertussis endpoints were redefined based on the assay cut-off (see section 5.7.5 of protocol).

- Note: Due to re-validation of all assays, the cut-offs presented in Table 7 of the protocol of few antigens have changed. Below table has an updated threshold.

Antigen	Threshold for positivity
• Anti-PT	• 2.693 IU/mL
• Anti-FHA	• 2.046 IU/mL
• Anti-PRN	• 2.187 IU/mL
• Anti-D	• 0.057 IU/mL
• Anti-T	• 0.043 IU/mL
• Anti-polio	• 8 dilution
• Anti-PRP	• 0.066 µg/mL
• Anti-HBs	• 6.2 mIU/mL
• Anti-pneumococcal serotypes (1)	• 0.080 µg/mL
• Anti-pneumococcal serotypes (3)	• 0.075 µg/mL
• Anti-pneumococcal serotypes (4)	• 0.061 µg/mL
• Anti-pneumococcal serotypes (5)	• 0.198 µg/mL
• Anti-pneumococcal serotypes (6A)	• 0.111 µg/mL
• Anti-pneumococcal serotypes (6B)	• 0.102 µg/mL
• Anti-pneumococcal serotypes (7F)	• 0.063 µg/mL
• Anti-pneumococcal serotypes (9V)	• 0.066 µg/mL
• Anti-pneumococcal serotypes (14)	• 0.160 µg/mL
• Anti-pneumococcal serotypes (18C)	• 0.111 µg/mL
• Anti-pneumococcal serotypes (19A)	• 0.199 µg/mL
• Anti-pneumococcal serotypes (19F)	• 0.163 µg/mL
• Anti-pneumococcal serotypes (23F)	• 0.073 µg/mL

- Also refer to the additional considerations section specific to each analysis of demography, immunogenicity and safety for additional updates to the planned analyses.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1 (Business rules for standard data derivations and statistical methods).

9.1. Data derivation

9.1.1. Congenital anomalies (CA)

Congenital anomalies (CA) are considered events of specific interest in maternal immunization programs and mostly recommended follow-up period seen in literature of infants born to mothers vaccinated during pregnancy is until 6 months of age. As per protocol, in Boostrix-047 study the follow-up period of infants after birth was two months. Hence, some CAs were not yet diagnosed and/or reported during the study Boostrix-047 and so these events have been reported in General Medical History section of infants in Boostrix-048 or in Boostrix-049 study. Given the importance of these safety data, medical coding of congenital anomalies reported in GMH section of Boostrix-048 (201330) and Boostrix-049 (201334) will be done. Since these CAs were not reported as SAEs and only the diagnosis code in verbatim was provided, the coding using the standard MedDRA query for the narrow CA will be performed.

An overview of all congenital anomalies both reported as unsolicited events and as pre-existing conditions in GMH section in these three studies will be present in Boostrix-049 study report, as this is the last study.

9.1.2. Ages & Stages Questionnaires (ASQ-3)

For the ASQ-3 analysis: The threshold value (cut off corresponding to the black zone) for each of the domain at time point month 9 and 18 are as follows [Squires, J., & Bricker, D., 2009].

Domain	Cut off (Month 9)	Cut off (Month 18)
Communication	13.97	13.06
Gross Motor	17.82	37.38
Fine motor	31.32	34.32
Problem Solving	28.72	25.74
Personal –Social	18.91	27.19

9.2. Statistical Method

If all subjects with ASQ-3 score in the black zone for at least one domain have BSID-III results, the clopper and Pearson CI will be used for the % of subjects with neurodevelopmental impairment.

If some subjects with ASQ-3 score in the black zone for at least one domain have no BSID-III results, the Greenwood formula [S.Sawyer,2003] for censored BSID-III data

will be used to estimate the % of subjects with neurodevelopmental impairment and associated CI.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

NA.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited symptoms

10.1.2.3.1. Studies with electronic diaries

NA.

10.1.2.3.2. Studies with paper diaries

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited symptoms, the following rules are applicable.

Denominators for the summary of local (or general) solicited symptoms will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of local (or general) symptoms.

When a specific symptom is marked as having not occurred following a specific vaccination for the specified post-vaccination period for the symptom in question, all daily measurements will be imputed as Grade 0.

When a specific symptom is marked as having occurred following a specific vaccination for the specified post-vaccination period for the symptom in question, any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

When the occurrence of a specific symptom is not present (for the specified post-vaccination period for the symptom in question) but the group of symptoms (local or general) is marked as having occurred, all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

The following table shows how subjects contribute to each category for a specific solicited symptom over the Day 0 to Day 3 post-vaccination period:

Solicited symptom category	Subjects included in the calculation of the numerator
Any	All subjects with at least one occurrence of the symptom at grade 1, grade 2, or grade 3 between Day 0 and Day 3 or with the symptom marked as present and at least one missing daily recording between Day 0 and Day 3
At least grade 1	All subjects with at least one occurrence of the symptom at grade 1, grade 2, or grade 3 between Day 0 and Day 3
At least grade 2	All subjects with at least one occurrence of the symptom at grade 2 or grade 3 between Day 0 and Day 3
At least grade 3	All subjects with at least one occurrence of the symptom at grade 3 between Day 0 and Day 3

For a given subject and the analysis of solicited adverse events within 4 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited adverse events based on the Total Vaccinated Cohort will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited adverse events after one dose will be considered not having that adverse events after that dose.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.

10.1.2.4. Unsolicited adverse events

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in months

When age at vaccination is to be displayed in months, it will be calculated as the number of complete calendar months between the date of birth (DOB) and the date of vaccination. For example:

DOB = 10JUN2017, Date of vaccination = 09JUL2018 -> Age = 12 months

DOB = 10JUN2017, Date of vaccination = 10JUL2018 -> Age = 13 months

10.1.3.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2. The result is rounded to 2 decimals.

10.1.3.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54 The result is rounded to the unit (ie no decimal).

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

10.1.3.5. Temperature

- Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

  Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

The result is rounded to 1 decimal.

- The intensity of fever measured by oral, axillary or tympanic route will be scored as defined in the protocol. If in case, measured by rectal route, then the scoring will be performed as below to integrate the results with the other routes.

0	<38°C
1	≥38.0°C to ≤39.0°C
2	>39.0°C to ≤40.0°C
3	>40.0°C

10.1.3.6. Numerical serology results

Numerical serology results will be derived Based on each assay cut-off (=LLOQ), using the following derivation rules

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

10.1.3.7. Geometric mean titres (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Antibody titres or concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.8. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

10.1.3.9. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the symptom reported at grade 1 or higher.

10.1.3.10. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered general events since the administration site flag is not included in the expedited adverse event CRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.11. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study vaccines, an injection site reaction recorded for a subject following multiple vaccines will be counted as only one occurrence.

10.1.4. Display of decimals

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

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
Immunogenicity	GMT/GMC	3 for anti-D, anti-T and anti-PRP 2 for Strepto antigens 1 for anti-PT, anti-FHA and anti-PRN, anti-HBs, anti-Polio 1, anti-Polio 2 and anti-Polio 3
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.2. TFL ToC

The TFL ToC can be found in eTMF folder section 11.1.1.

11. REFERENCES

Clopper CJ, Pearson E. (1934), The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. Biometrika.

S.Sawyer (2003), The Greenwood and Exponential Greenwood Confidence Intervals in Survival Analysis.

Squires, J., & Bricker, D. (2009), Ages & Stages Questionnaires, Third Edition (ASQ-3). Baltimore, MD: Brookes Publishing.

12. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following drafted study specific mocks will be used.

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

These templates were copied from recent studies. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require a SAP amendment.

Template 1 Number of subjects enrolled by center (Total vaccinated cohort)

	dTpa Group	Control group	Total	
Center	**n**	**N**	**n**	**%**
PPD				
PPD				
PPD				
PPD				
PPD				
PPD				
PPD				
PPD				
PPD				
PPD				
PPD				
All				

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
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 enrolled by country (Total vaccinated cohort)

	dTpa Group	Control group	Total	
Country	**n**	**N**	**n**	**%**
Australia				
Belgium				
Canada				
Czechia				
Finland				
Italy				
Spain				
All				

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
n = number of subjects included in each group or in total for a given country or for all countries
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100

Template 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

	dTpa Group	Control Group	Total
Number of subjects vaccinated			
Number of subjects completed			
Number of subjects withdrawn			
Reasons for withdrawal:			
Serious Adverse Event			
Non-serious adverse event			
Protocol violation			
Consent withdrawal (not due to an adverse event)			
Migrated/moved from study area			
Lost to follow-up (subjects with incomplete vaccination course)			
Lost to follow-up (subjects with complete vaccination course)			
Others			

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for last study visit

Template 4 Number of subjects at each visit and list of withdrawn subjects (Total Vaccinated Cohort)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
dTpa Group	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
Control Group	VISIT 1	257		
			no. PP	PROTOCOL VIOLATION
			no. PPD	CONSENT WITHDRAWAL
	VISIT 2	255		

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
			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

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
N = number of subjects who are still in the study up to the visit
Withdrawn = subject who did not return after the visit

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

	Total				dTpa Group			Control Group		
Title	**N**	**n**	**s**	**%**	**N**	**n**	**s**	**N**	**n**	**s**
Total enrolled cohort	**1200**				**300**			**300**		
Invalid informed consent or fraud data (code 900)										
Study vaccine dose not administered AT ALL but subject number allocated (code 1030)										
TVC	**1200**			**100**	**300**			**300**		
Administration of vaccine(s) forbidden in the protocol (code 1040)		2	2			0	0		0	0
Randomisation code broken at the investigator site OR at GSK Safety department (1060)										
Study vaccine dose not administered according to protocol (code 1070)		73	73			23	23		16	16
Vaccine temperature deviation (code 1080)										
Expired vaccine administered (code 1090)		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 related to the vaccine which may influence immune response (2060)										
Concomitant infection not related to the vaccine which may influence immune response (code 2070)		0	1			0	0		0	1
Noncompliance with vaccination schedule (including wrong and unknown dates) (code 2080)		14	16			6	7		3	4
Noncompliance 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
Obvious incoherence, abnormal serology evolution or error in data (code 2120)		1	1			0	0		0	0
ATP cohort for analysis of immunogenicity	**998**			**83.2**	**244**			**252**		

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Note: Subjects may have more than 1 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 6 Deviations from specifications for age and intervals between study visits for subjects vaccinated with Infanrix hexa(<2> dose schedule - 1 dose/visit) (Total Vaccinated Cohort)

		Age	VAC_1-SER_2	
Group		**Protocol**	**Protocol**	**Adapted**
		DOB to vaccination is 11-18months of age*	from 30 to 48 days	from 21 to 48 days
dTpa 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
Control 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

		Age	VAC:1-VAC:2	VAC:2-SER:2
Group		**Protocol**	**Protocol**	**Protocol**
		from 6 to 14 weeks and 6 days	from 52 to 78 days	from 21 to 48 days
dTpa Group	N			
	n			
	%			
	range			
Control Group	N			
	n			
	%			
	range			

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
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:1 = vaccination at visit 1
VAC:2 = vaccination at visit 2
SER:2 = blood sample collected before the first dose and 1 month after the last dose of the primary vaccination course
2 dose schedule = subjects who received 2 dose of *Infanrix hexa* at 2,4 months of age or 3,5 months of age, co-administered with *Prevenar 13* (according to the routine national immunisation schedule of the country).
* Window from DOB to vaccination is 11-18(+30 days) months of age according to the routine national/ local immunization schedule or as specified in the SPM

Template 7 Summary of demographic characteristics (Total vaccinated cohort)

		dTpa Group N =		Control Group N =		Total N =	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (week) at vaccination dose: 1	Mean						
	SD						
	Median						
	Q1						
	Q3						
Gender	Female						
	Male						
Geographic Ancestry	African Heritage / African American						
	American Indian or Alaskan Native						
	Asian - Central / South Asian Heritage						
	Asian - East Asian Heritage						
	Asian - Japanese Heritage						
	Asian - South East Asian Heritage						
	Native Hawaiian or Other Pacific Islander						
	White - Arabic / North African Heritage						
	White - Caucasian / European Heritage						
	Other (Hispanic)						
Dose schedule	2 dose schedule						
	3 dose schedule						
Maternal age group	18-24Y						
	25-34Y						
	35-45Y						
Gestational week of foetus at dose 1	27-32W						
	33-36W						

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
N = total number of subjects
n(%) = number(percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Q1 = Quartile 1
Q2 = Quartile 3
2 dose schedule = subjects who received 2 dose of Infanrix hexa at 2,4 months of age or 3,5 months of age, co-administered with Prevenar 13 (according to the routine national immunisation schedule of the country).
3 dose schedule = subjects who received 3 dose of Infanrix hexa at 2,3,4 months of age or 2,4,6 months of age, co-administered with Prevenar 13.Prevenar 13 could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule of the country).
18-24Y = 18-24 years old subjects
25-34Y = 25-34 years old subjects
35-45Y = 35-45 years old subjects
27-32W = 27-32 weeks of gestation of foetus at dose 1
33-36W = 33-36 weeks of gestation of foetus at dose 1

Template 8 Summary of vital signs characteristics (Total Vaccinated Cohort)

		dTpa Group (N = 335)	Control Group (N = 336)	Total (N = 671)
Characteristics	**Parameters**	**Value**	**Value**	**Value**
Height (cm)	Mean			
	SD			
	Median			
	Q1			
	Q3			
	Unknown			
Weight (kg)	Mean			
	SD			
	Median			
	Q1			
	Q3			
	Unknown			
Head circumference (cm)	Mean			
	SD			
	Median			
	Q1			
	Q3			
	Unknown			
Body mass index in [kg/m2]	Mean			
	SD			
	Median			
	Q1			
	Q3			
	Unknown			

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
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
Head circumference(cm) = head circumference expressed in centimeters.
Body mass index in [kg/m2] = body mass index expressed in kilograms per meter square
SD = standard deviation
Q1 = Quartile 1
Q2 = Quartile 3

Template 9 Study population (TVC)

Study population (Total vaccinated cohort)		
Number of subjects	**dTpa group**	**Control group**
Planned, N	225	225
Randomised, N (Total Vaccinated Cohort)	224	227
Completed, n (%)	224 (100)	227 (100)
Demographics	**dTpa 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)

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
N = total number of subjects enrolled in the study
n/% = number/percentage of subjects in a given category
SD = Standard Deviation
Mean Age = age calculated from Date of birth to first study vaccination

Template 10 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies before the first dose and 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥ assay cut-off*				**GMC**		
									95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PT	dTpa Group	Pre-Pri								
		Post-Pri								
	Control Group	Pre-Pri								
		Post-Pri								
Anti-FHA	dTpa Group	Pre-Pri								
		Post-Pri								
	Control Group	Pre-Pri								
		Post-Pri								
Anti-PRN	dTpa Group	Pre-Pri								
		Post-Pri								
	Control Group	Pre-Pri								
		Post-Pri								

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
*Assay cut-off is 2.693 IU/mL for anti- PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN
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 = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = blood sample to be collected 1 month after the last dose of the primary vaccination course

Template 11 Seropositivity, seroprotection and GMC rates for <anti-tetanus> antibodies before the first dose and 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥ assay cut-off*				≥ 0.1 IU/mL				≥ 1.0 IU/mL				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**UL**	**UL**	**value**	**LL**	**UL**
Anti-tetanus	dTpa Group	Pre-Pri																
		Post-Pri																
	Control Group	Pre-Pri																
		Post-Pri																
Anti-diphtheria	dTpa Group	Pre-Pri																
		Post-Pri																
	Control Group	Pre-Pri																
		Post-Pri																

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
*Assay cut-off is 0.043 IU/mL for anti-tetanus and 0.057 IU/mL for anti- diphtheria
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 = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = blood sample to be collected 1 month after the last dose of the primary vaccination course

Template 12 Seroprotection rates for anti-poliovirus type 1,2,3 antibodies before the first dose and 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**UL**	**UL**	**value**	**LL**	**UL**
anti-poliovirus type 1	dTpa Group	Pre-Pri								
		Post-Pri								
	Control Group	Pre-Pri								
		Post-Pri								
anti-poliovirus type 2	dTpa Group	Pre-Pri								
		Post-Pri								
	Control Group	Pre-Pri								
		Post-Pri								
anti-poliovirus type 3	dTpa Group	Pre-Pri								
		Post-Pri								
	Control Group	Pre-Pri								
		Post-Pri								

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMT = 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 = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = blood sample to be collected 1 month after the last dose of the primary vaccination course

Template 13 Booster responses for anti-PT, anti-FHA and anti-PRN antibody concentration 1 month after the last dose of the primary vaccination course (ATP cohort for immunogenicity)

				Vaccine response			
						95% CI	
Antibody	**Group**	**Pre-Pri* status**	**N**	**n**	**%**	**LL**	**UL**
anti-PT	dTpa Group	S-					
		S+ (≥cut-off IU/mL)					
		Total					
	Control Group	S-					
		S+ (≥cut-off IU/mL)					
		Total					
anti-FHA	dTpa Group	S-					
		S+ (≥cut-off IU/mL)					
		Total					
	Control Group	S-					
		S+ (≥cut-off IU/mL)					
		Total					
anti-PRN	dTpa Group	S-					
		S+ (≥cut-off IU/mL)					
		Total					
	Control Group	S-					
		S+ (≥cut-off IU/mL)					
		Total					

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.

Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.

S- = Initially seronegative subjects (antibody concentration below assay cut-off for anti-PT, anti-FHA, anti-PRN)

S+ = Initially seropositive (antibody concentration above assay cut-off for anti-PT, anti-FHA, anti-PRN)

Total = subjects either seropositive or ser1gative at pre-vaccination

Booster response to the PT, FHA and PRN antigens, is defined as:

- initially seronegative subjects (pre-booster antibody concentration below cut-off: < 5ELISA EL.U/mL) with an increase of at least four times the cut-off one month after vaccination (post-booster antibody concentration ≥ 20 EL.U/mL), and
- initially seropositive subjects with pre-booster antibody concentration ≥ 5EL.U./mL and < 20EL.U/mL with an increase of at least four times the pre-booster antibody concentration one month after vaccination, and,
- For initially seropositive subjects with pre-booster antibody concentration ≥20EL.U/mL with an increase of at least two times the pre-booster antibody concentration, one month after vaccination.

N = number of subjects with pre- and post-vaccination results available

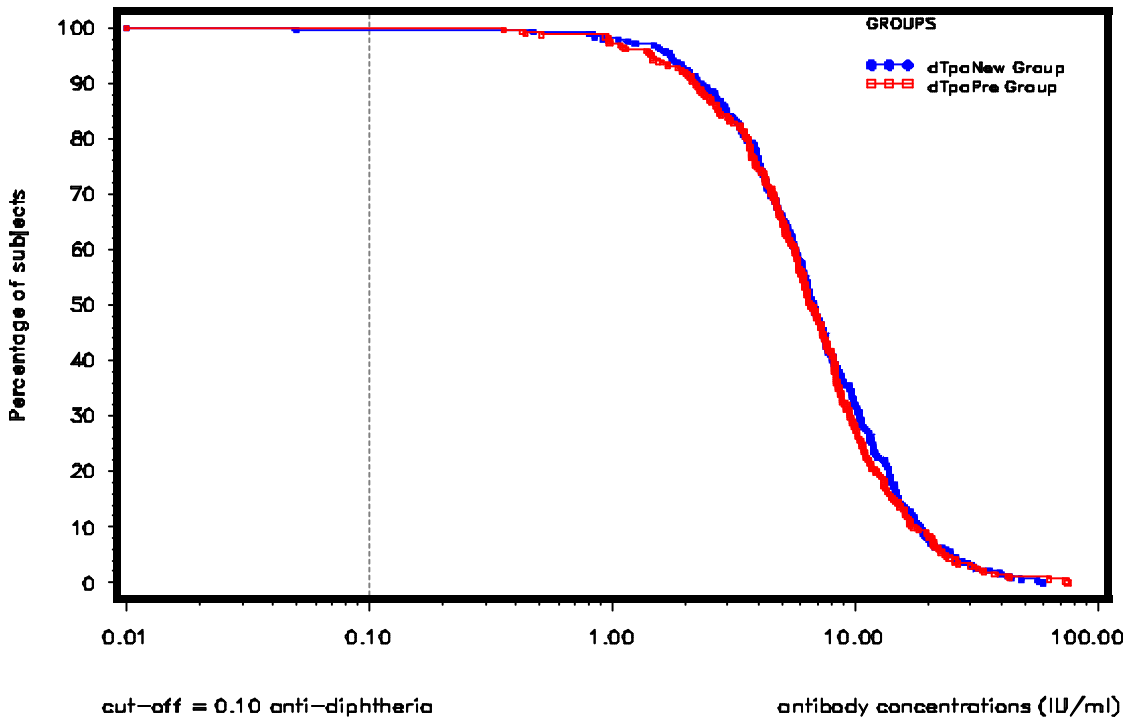
n(%) = number(percentage) of subjects with booster response

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

*Pre-Pri = blood sample to be collected before the first dose of the primary vaccination course

Note: The assay cut-off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Template 14 Reverse cumulative curve for anti-diphtheria antibody concentration before first dose and 1 month post last dose of the primary vaccination course (ATP cohort for immunogenicity)



dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Pre-Pri = blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = blood sample to be collected 1 month after the last dose of the primary vaccination course
Note: The groups shown in figure are indicative only. Actual groups may differ.

Template 15 Number and percentage of subjects who received the study vaccine dose by vaccination group (Total vaccinated cohort)

		dTpa group N =		Control group N =		Total N = 1200	
VACCINE	**Total number of doses received**	**n**	**%**	**n**	**%**	**n**	**%**
Pediarix	1						
	2						
	3						
Any	Any						
Hiberix	1						
	2						
	3						
Any	Any						
Prevnar	1						
	2						
	3						
Any ON COAD	Any						

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
N = number of subjects in each group or in total included in the considered cohort
n(%) = number(percentage) of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least 1 dose

Template 16 Compliance in returning symptom sheets (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**
dTpa Group	335	0	330	98.5	330	98.5
Control Group	336	1	329	97.9	329	97.9

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
SS = Symptom sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100

Template 17 Percentage and nature of <grade 3>symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
dTpa 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
Control 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

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
For each dose and overall/subject:
N= number of subjects with at least 1 administered dose
n(%) = number(percentage) of subjects presenting at least 1 type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n(%) = number(percentage) of doses followed by at least 1 type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 18 Percentage of solicited local symptoms reported during the 4-day (Day 0-3) post-vaccination period following each dose and overall (Total vaccinated cohort)

		dTpa group					Control 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

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
For overall/subject:
N= number of subjects with at least 1 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 19 Percentage of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall (Total vaccinated cohort)

		dTpa group					Control group				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/subject											
Drowsiness	All										
	Grade 2 or 3										
	Grade 3										
	Related										
	Grade 3*Related										
	Medical advice										
Irritability	All										
	Grade 2 or 3										
	Grade 3										
	Related										
	Grade 3*Related										
	Medical advice										
Loss of appetite	All										
	Grade 2 or 3										
	Grade 3										
	Related										
	Grade 3*Related										
	Medical advice										
Temperature/(Axillary) (°C)	All										
	>37.5										
	>38.0										
	>38.5										
	>39.0										
	>39.5										
	Related										
	>39*Related										
	Medical advice										

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule. For each dose and overall/subject:
N= number of subjects with at least 1 documented dose
n(%) = number(percentage) of subjects reporting the symptom at least once
For overall/subject:
N= number of subjects with at least 1 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

Template 20 Percentage of Unsolicited symptoms experienced by subjects classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) after the booster dose (Total vaccinated cohort)

		dTpa Group N =			Control Group N =		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
At least 1 symptom							
<each SOC>	<each PT term>						

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule. For each dose and overall/subject:
At least 1 symptom = at least 1 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 21 Number (%) of subjects with serious adverse events from the Day 0 to end of the study (Total Vaccinated cohort)

Type of Event	**Primary System Organ Class**	**Preferred Term (CODE)**	**dTpa Group N =**			**Control Group N =**		
			n*	**n**	**%**	**n***	**n**	**%**
SAE	At least 1 symptom							
	<each SOC>	<each PT>						
Related SAE	At least 1 symptom							
	<each SOC>	<each PT>						
Fatal SAE	At least 1 symptom							
	<each SOC>	<each PT>						
Related Fatal SAE	At least 1 symptom							
	<each SOC>	<each PT>						

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule. For each dose and overall/subject:
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 22 Solicited and unsolicited adverse events 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)

		dTpa Group N =			Control Group N =		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
At least 1 symptom							
<each SOC>	<each PT term>						

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule. For each dose and overall/subject:
At least 1 symptom = at least 1 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

Template 23 Number and percentage of subjects taking a concomitant medication and antipyretic medication during the 4-day (Days 0-3) follow-up period post-vaccination by dose and overall (Total vaccinated cohort)

	dTpa group					Control group				
				95% CI					95% CI	
	N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Overall/subject										
Any										
Any antipyretic										
Prophylactic antipyretic										

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule. For each dose and overall/subject:
For overall/subject:
N= number of subjects with at least 1 administered dose
n(%) = number(percentage) of subjects who started to take the specified concomitant medication at least once during the menti1d period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 24 Minimum and maximum activity dates (Total vaccinated cohort)

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

Database Lock Date = 31MAR2009

Template 25 Number of enrolled subjects by age category at visit 1

		dTpa group N =	Control group N =	Total N =
Characteristics	**Categories**	**n**	**n**	**n**
Age category	Infants (6 weeks – 14 weeks and 6 days)			
	Missing			

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule. For each dose and overall/subject:
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 = subjects who are enrolled in the study but not vaccinated and for which age is unknown

Template 26 Listing of SAEs from Day 0 up study (Total vaccinated cohort)

Group	Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MED type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
dTpa group														
Control group														

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule
Med type = Type of medical advice; HO= Hospitalisation, ER = Emergency room

Template 27 Listing of dropouts due to AEs, SAEs and solicited symptoms (Total vaccinated cohort)

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

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule

Template 28 Listing of large injection site swelling reaction (Total Vaccinated Cohort)

Sub. No.	Group	Subject number	Dose	Day of onset	Size (mm)	Type of swelling	Circumference of swollen limb (mm)	Duration (days)	Outcome

dTpa Group = This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule

Template 29 Percentage of subjects with ASQ-3 score in the black zone for Month 9, 18 (Total enrolled cohort)

			dTpa Group					Control Group				
						95% CI					95% CI	
Time point	**Characteristics**	**Categories**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Month 9	Any domain	Yes										
		No										
	Communication	Yes										
		No										
	Fine motor	Yes										
		No										
	Problem solving	Yes										
		No										
	Personal-Social	Yes										
		No										
Month 18	Any domain	No										
	Communication	Yes										
		No										
	Fine motor	Yes										
		No										
	Problem solving	Yes										
		No										
	Personal-Social	Yes										
	Personal-Social	Yes										
		No										
Month 9 or 18	Any domain	No										
	Communication	Yes										
		No										
	Fine motor	Yes										
		No										
	Problem solving	Yes										
		No										
	Personal-Social	Yes										

			dTpa Group					Control Group				
						95% CI					95% CI	
Time point	**Characteristics**	**Categories**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
	Personal-Social	Yes										
	Personal-Social											

dTpa Group = Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy. All subjects in this group will receive Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
Control Group = Infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy. All subjects in this group will receive Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
N = number of subjects enrolled
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
LL, UL for percentage = Exact 95% Lower and Upper confidence limits

Template 30 Percentage of subjects with confirmed developmental delay as determined by BSID-III at Month 9, 18 (Total enrolled cohort)

			dTpa Group					Control Group				
						95% CI					95% CI	
Time point	Characteristics	Categories	N	n	%	LL	UL	N	n	%	LL	UL
Month 9	Any domain	Yes										
		No										
		Missing										
	Cognitive	Yes										
		No										
		Missing										
	Language	Yes										
		No										
		Missing										
	Motor	Yes										
		No										
		Missing										
	Emotional	Yes										
		No										
		Missing										
	Behaviour	Yes										
		No										
		Missing										
Month 18	Any domain	Yes										
		No										
		Missing										
	Cognitive	Yes										
		No										
		Missing										
	Language	Yes										
		No										
		Missing										
	Motor	Yes										
		No										
		Missing										
	Emotional	Yes										
		No										
		Missing										
	Behaviour	Yes										
		No										
		Missing										
Month 9 or 18	Any domain	Yes										
		No										
		Missing										
	Cognitive	Yes										
		No										
		Missing										
	Language	Yes										
		No										
		Missing										
	Motor	Yes										
		No										
		Missing										

			dTpa Group					Control Group				
						95% CI					95% CI	
Time point	**Characteristics**	**Categories**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
	Emotional	Yes										
		No										
		Missing										
	Behaviour	Yes										
		No										
		Missing										

dTpa Group = Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy. All subjects in this group will receive Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
Control Group = Infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy. All subjects in this group will receive Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
N = number of subjects enrolled
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Missing: number of subjects with ASQ-3 score in the black zone which are not referred for the BSID III

Template 31 Proportion of subjects with neurodevelopmental delay (Total enrolled cohort)

			ASQ-3 score in the black zone for at least one domain		At least one of the indicators of neurodevelopmental delay using BSID III among the infants referred for BSID III evaluation		Estimated proportion of infants with at least one of the indicators of neurodevelopmental delay using BSID-III			
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**LL**	**UL**
DTPa group	Month 9									
	Month 18									
	Month 9 or 18									
Control group	Month 9									
	Month 18									
	Month 9 or 18									

N = number of subjects enrolled
n/N = number of subjects with ASQ-3 below cut off / number of enrolled subjects
n'/N' = number of subjects with at least one indicator of neurodevelopmental delay using BSID III / number of subjects referred for BSID III evaluation
% = proportion of subjects with neurodevelopmental impairment at x time point
n/N x n'/N' = the multiplication of the two proportions
95% CI = exact 95% confidence interval (Clopper Pearson or Greenwood formula); LL = lower limit, UL = upper limit

Template 32 Evolution graph for the pertussis antibodies (Adapted ATP cohort)