Clinical Study Protocol
Sponsor
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium.

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b (DTPa-HBV-IPV/Hib) vaccine (Infanrix hexa™) (217744).
Other Study vaccine	Pneumoccocal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Prevenar 13®, Manufactured by Wyeth Pharmaceuticals Inc. Marketed by Pfizer Inc.).
eTrack study number and Abbreviated Title	201334 [DTPA (BOOSTRIX)-049 BST: 048]
EudraCT number	2014-001120-30
Date of protocol	Final Version 2: 14 March 2016
Date of protocol amendment	Amendment 1 Final 12 December 2016
Title	Immunogenicity and safety study of a booster dose of GSK Biologicals' Infanrix hexa™ (217744) in healthy infants born to mothers vaccinated with Boostrix™ during pregnancy or immediately post-delivery.
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.
Co-ordinating authors	PPD, Scientific Writers
Contributing authors (Amended 12 December 2016)	• PPD, ***Clinical and Epidemiology Project Leader (CEPL)*** • PPD, Clinical Research and Development Lead (CRDL) • PPD ***and*** PPD, Clinical Research and Development Lead (Project-Level CRDL) • PPD, Project Statistician • PPD ***and*** PPD, Study Delivery Lead • PPD, PPD, Clinical Laboratory Sciences (CLS) Clinical Read-Out Team Leader

eTrack study number and Abbreviated Title	201334 [DTPA (BOOSTRIX)-049 BST: 048]
EudraCT number	2014-001120-30
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.
Contributing authors	• PPD, ***CLS Study Manager*** • PPD ***and*** PPD, Global Clinical Regulatory Affairs Representative • PPD, PPD, PPD and PPD, Clinical Safety Representatives • PPD, Global Patents Representative • PPD, Study Data Manager • PPD, PPD, ***Oversight data Manager*** • PPD ***and*** PPD, Senior Manager, Biometrics • PPD ***and*** PPD, Vaccines Supply Coordinator • PPD, Director, Global Medical Affairs • PPD, Study Delivery Manager • PPD ***and*** PPD, Local Delivery Lead, Australia • PPD ***and*** PPD, Local Delivery Lead, Canada • PPD ***and*** PPD Local Delivery Lead, Spain • PPD ***and*** PPD, Local Delivery Lead, Czech Republic • PPD, Director/Local Medical Lead, Czech Republic • PPD, ***Local Delivery Lead, Finland*** • PPD ***and*** PPD, ***Local Delivery Leads, Italy***

GSK Biologicals' Protocol DS v 14.1.1

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	201334 [DTPA (BOOSTRIX)-049 BST: 048]
EudraCT number	2014-001120-30
Date of protocol amendment	Amendment 1 Final: 12 December 2016
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.
Sponsor signatory	Narcisa Mesaros, MD Clinical and Epidemiology R&D Project Leader (CEPL), DTP, Polio, Hib containing vaccines R&D Center Belgium
Signature	_____
Date	_____

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	201334 [DTPA (BOOSTRIX)-049 BST: 048]
EudraCT number	2014-001120-30
Date of protocol amendment	Amendment 1 Final: 12 December 2016
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.
Sponsor signatory	Narcisa Mesaros, MD Clinical and Epidemiology R&D Project Leader (CEPL), DTP, Polio, Hib containing vaccines R&D Center Belgium
Signature	PPD
Date	22 Dec 2016

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Protocol Amendment 1 Rationale

Amendment number: Amendment 1

Rationale/background for changes:

Given the fact that only infants born from mothers vaccinated in the study (116945 [DTPA (BOOSTRIX)-047) and vaccinated in the previous study 201330 [DTPA (BOOSTRIX)-048 PRI] can be enrolled in the current study, the enrolment in these studies has an impact on this current study (e.g. cohorts to be investigated). Initially, the DTPA (BOOSTRIX)-047 and DTPA (BOOSTRIX)-048 PRI studies were opened only in countries using 3-dose primary vaccination series plus a booster vaccination at 12 to 18 months of age against diphtheria, tetanus and pertussis in infants. Nevertheless, the 2-dose primary vaccination schedule with a booster vaccination at 11 to 13 months of age in infants is also meaningful for different regions in the world (e.g. Europe). It was therefore decided to open the DTPA (BOOSTRIX)-047 and DTPA (BOOSTRIX)-048 PRI, and therefore the current booster study to countries using 2-dose primary vaccination series with a booster vaccination at 11 to 13 months of age with the aim to increase the scientific value of the study and generate clinical data in diverse infant vaccination schedules. This protocol is amended to include the possibility to administer the booster vaccine dose at 11 to 13 months of age, in addition to the 12 to 18 months of age initially planned.

The notion of end of study was clarified and the Section 11.5 describing the posting of information on public registry was revised accordingly.

An inclusion criterion was updated to specify that only infant having received the full vaccination series as per protocol requirement in the study DTPA (BOOSTRIX)-048 PRI can be enrolled in the current study (and not only infant born from mother vaccinated in the DTPA (BOOSTRIX)-047).

Following a request from the Czech Republic, the phone call at 18 months may be replaced by a clinic visit if deemed preferable by the study team.

The vaccination sites were updated to allow vaccination either in the thigh or deltoid, according to the national recommendation, to comply with the Australian recommendations.

The names and functions of the contributing authors have been updated. In addition, minor updates including typos, abbreviations, clarifications of wording were done throughout the document.

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational vaccine and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	201334 [DTPA (BOOSTRIX)-049 BST: 048]
EudraCT number	2014-001120-30
Date of protocol Amendment	Amendment 1 Final: 12 December 2016
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.
Investigator name	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium.

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.2.

SYNOPSIS

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.
Indication	Booster immunisation of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b (Hib).
Rationale for the study and study design	• Rationale for the study Recent studies have shown that maternal combined reduced antigen content diphtheria-tetanus-acellular pertussis (dTpa) vaccination during pregnancy results in high pertussis antibody concentrations in infants during the period between birth and the first vaccine dose. Although slightly decreased immune responses following the primary diphtheria-tetanus-acellular pertussis (DTPa) vaccination has been observed in infants whose mothers received dTpa vaccine compared to those whose mothers did not receive dTpa vaccine, the differences did not persist following the booster vaccination in infants [Hardy-Fairbanks, 2013; Gall, 2011]. An analysis of data from the Clinical Practice Research Datalink (a primary care database of 520 general medical practices in England) demonstrates that maternal dTpa immunisation can decrease the incidence of infant pertussis. After a maternal pertussis vaccination programme was introduced in October 2012 in response to a pertussis outbreak in England, the number of pertussis cases in infants younger than three months of age and the number of hospitalisations decreased significantly [Amirthalingam, 2014]. In 2013, the Advisory Committee on Immunization Practices (ACIP) recommended that all women should be vaccinated with dTpa vaccine during each pregnancy, regardless of the previous immunisation schedule [CDC, 2013]. Similar recommendations have been implemented in 18 countries including United Kingdom, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica, Argentina, Australia and some provinces in Spain [Joint Committee on Vaccination and Immunization (JCVI), 2012; Pharmaceutical Management Agency (PHARMAC), 2012; TAG, 2013]. The National Advisory Committee on Immunization in Canada recommends that all pregnant women following 26 weeks of pregnancy who have not received a dose of pertussis-containing vaccine in adulthood should be encouraged to

receive dTpa vaccination. In special circumstances, such as an outbreak situation, all pregnant women who are of 26 weeks gestation or greater may be offered dTpa vaccination irrespective of their immunisation history [Warshawsky, 2014; Public Health Agency of Canada, 2014].

All infants born to pregnant women who participated in study 116945 [DTPA (BOOSTRIX)-047] will be followed-up to study the immunogenicity and safety of GSK Biologicals' combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b vaccine (DTPa-HBV-IPV/Hib)*, Infanrix hexa,* given as primary and booster vaccination. Study 201330 [DTPA (BOOSTRIX)-048 PRI] will be conducted to assess the immunogenicity and safety of *Infanrix hexa* co-administered with *Prevenar 13* as the primary vaccination course.

The present study will be performed to study the immunogenicity and safety of the booster dose of *Infanrix hexa* in infants who were born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery ***and who completed their primary vaccination series as per protocol requirement in study DTPA (BOOSTRIX)-048 PRI.*** **(Amended 12 December 2016)**

- Rationale for the study design

This phase IV study is a follow-up of the study 201330 [DTPA (BOOSTRIX)-048 PRI]. The immunogenicity and safety of *Infanrix hexa* when given as a booster dose ***according to the routine national/ local immunization schedule or as specified in the SPM*** will be evaluated. Subjects will receive *Prevenar 13* ***according to the routine national/ local immunization schedule or as specified in the SPM*** as a co-administered vaccine in this study. **(Amended 12 December 2016)**

This study will have two groups:

- 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 infants 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***. **(Amended 12 December 2016)**

- 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 infants 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***. **(Amended 12 December 2016)**

The study will be open-label since the treatment allocation is similar between the two groups. Also, the data related to the study groups will be unblinded at the end of study 116945 [DTPA (BOOSTRIX)-047].

Currently, the effect of *Boostrix* administered to mothers during pregnancy or immediately post-delivery on the neurodevelopment of infants is unknown. Therefore, the neurodevelopment of the subjects will be studied at 9 months and 18 months of age in this study. To assess the neurodevelopmental status, the ***investigator or designate*** will complete a standardised developmental screening tool, Ages and Stages Questionnaire-3 (ASQ-3) via a paper questionnaire ***with subjects' parent(s)/LAR(s) during the study visits or phone call*** [ASQ-3, 2016]. **(Amended 12 December 2016)**

Any subject who scores below the cut-off i.e., a score more than 2 Standard Deviations (SDs) below the mean score for the U.S. reference group (i.e., black zone in the score chart) in any of the five domains of the ASQ-3 (i.e., communication, gross motor, fine motor, problem solving, and personal-social) will be referred to a developmental specialist for formal neurodevelopmental assessment (e.g., using the Bayley Scale for Infant Development, Version III [BSID-III]) [Bayley-III, 2006]. An overall neurodevelopmental assessment in the areas of cognitive, language, motor, social-emotional and adaptive behaviour will be rendered using BSID-III. A BSID-III score more than 2 SDs below the mean score for the U.S. reference group will be considered as a neurodevelopmental impairment.

Objectives

Primary

- 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.

Secondary

- 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.

Study design

- 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. **(Amended 12 December 2016)**
- ***End of Study (EoS): Last testing results released of samples collected at Visit 3.*** **(Amended 12 December 2016)**
- Study groups: The study groups and epoch foreseen in the study are presented in Synopsis 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*** vaccination course 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***. **(Amended 12 December 2016)**.

– 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*** vaccination course 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***. **(Amended 12 December 2016)**.

Synopsis Table 1 Study groups and epoch foreseen in the study

(Amended 12 December 2016)

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

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

The study groups and treatment foreseen in this study are given in Synopsis Table 2.

Synopsis Table 2 Study groups and treatment foreseen in the study

(Amended 12 December 2016)

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***. **(Amended 12 December 2016)**

- 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 SBIR and the site staff will remain blinded towards the treatment allocation ***of the mother in*** study 116945 [DTPA (BOOSTRIX)-047]. **(Amended 12 December 2016)**

The blinding of the study is given in Synopsis Table 3.

Synopsis 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 adverse events (AEs), unsolicited AEs will be reviewed by this committee ***as per approved IDMC charter***. **(Amended 12 December 2016)**

Number of subjects A maximum of 680 infants (approximately 340 infants in each group) aged 9 months will be enrolled in this study. Blood samples will be taken from all subjects in order to evaluate the immunogenicity endpoints.

Endpoints

Primary

- 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.

Secondary

- 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, 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.

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LIST OF ABBREVIATIONS

(Amended 12 December 2016)

ACIP:	Advisory Committee on Immunization Practices
AE:	Adverse Event
Anti-HBs:	Antibodies against hepatitis B surface antigen
ASQ-3:	Ages and Stages Questionnaire-3
ATP:	According-To-Protocol
BSID-III:	Bayley Scale for Infant Development, Version III
CDC:	Centers for Disease Control and Prevention, USA
CI:	Confidence Interval
CLIA:	ChemiLuminescence ImmunoAssay
CLS:	Clinical Laboratory Sciences
CRDL:	***Clinical Research and Development Lead***
DTP:	Diphtheria-Tetanus-Pertussis
dTpa:	Combined reduced antigen content diphtheria-tetanus-acellular pertussis vaccine
DTPa:	Diphtheria-Tetanus-acellular Pertussis
DTPA-HBV-IPV/Hib:	Combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b vaccine (*Infanrix hexa*)
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked ImmunoSorbent Assay
EL.U/mL:	***ELISA Unit per milliter***
EoS:	***End of Study***
EPAR:	***European public assessment report***
FHA:	Filamentous Haemagglutinin
GCP:	***Good Clinical Practice***

GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titre
GSK:	GlaxoSmithKline
HBs:	Hepatitis B surface antigen
HBV:	Hepatitis B Virus
HHE:	***Hypotonic-Hyporesponsiveness Episode***
Hib:	*Haemophilus influenzae* type b
HIV:	***Human Immunodeficiency Virus***
IB:	***Investigator Brochure***
ICF:	***Informed Consent Form***
ICH:	***International Conference on Harmonization***
IDMC:	Independent Data Monitoring Committee
IEC:	***Independent Ethics Committee***
IgG/ IgM:	***Immunoglobulin G/ M***
IM:	***Intramuscular***
IMP:	***Investigational Medicinal Products***
IPV:	Inactivated Poliovirus Vaccine
IRB:	***Institutional Review Board***
JCVI:	***Joint Committee on Vaccination and Immunization***
LAR:	Legally Acceptable Representative
LL:	***Lower Limit***
LSLV:	***Last Subject Last Visit***
MedDRA:	Medical Dictionary for Regulatory Activities
(m)IU:	*(*Milli*)*-international units
PI:	***Product Information***

PRN:	Pertactin
PRP:	Hib capsular polysaccharide Polyribosyl-Ribitol Phosphate
PT:	Pertussis Toxoid
RCC:	***Reverse Cumulative Curve***
RSI:	***Reference Safety Safety Information***
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SD:	Standard Deviation
SDV:	***Source Document Verification***
SIDS:	***Sudden Infant Death Syndrome***
SPC:	***Summary of Product characteristics***
SPM:	***Study Procedure Manual***
SRT:	***Safety Review Team***
(e)TDF:	***(electronic) Temperature Excursion decision Form***
TT:	Tetanus Toxoid
TVC:	Total Vaccinated Cohort
UK:	***United Kingdom***
UL:	***Upper Limit***
USA:	United States of America
WHO:	World Health Organization

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study: ***(Synonym of End of Trial)*** **(Amended 12 December 2016)**	***For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV).*** ***For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV***

Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.7.2 and 10.4 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Legally acceptable representative: **(The terms legal representative or legally authorised representative are used in some settings.)**	An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively

	solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Infanrix hexa™	Combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus vaccine and *Haemophilus influenzae* type b conjugate vaccine

(Amended 12 December 2016)

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Prevenar 13® (Wyeth Pharmaceuticals Inc.; Marketed by Pfizer Inc. or ***Wyeth LLC, owner/Pfizer Canada Inc., Licensee***)	***Pneumococcal*** 13-valent conjugate vaccine (diphtheria CRM_{197} protein)

1. INTRODUCTION

1.1. Background

Infants experience the highest rates of serious complications, hospitalisations and death due to pertussis. This is mainly because they are too young to have completed the primary diphtheria, tetanus and acellular pertussis (DTPa) immunisation series.

Since 2000, most deaths and hospitalisations related to pertussis have been in unvaccinated infants younger than three months of age [Murphy, 2008]. In 2012, there were 48,777 reported cases of pertussis in the United States (US). Infants younger than one year of age had the highest incidence compared to other studied age groups. Fifteen out of 20 deaths occurred in unvaccinated infants younger than three months of age. In 2014, there were 28,660 reported cases of pertussis in the US. The incidence again was highest in infants younger than one year of age and all of nine deaths due to pertussis occurred in unvaccinated infants three months of age and younger [***Centers for Disease Control and Prevention (***CDC), 2015; CDC, 2013]. **(Amended 12 December 2016)**

In Canada, approximately 2500 cases were reported in 2012 [Public Health Agency of Canada, 2012]. The United Kingdom (UK) was amidst a large outbreak of pertussis in 2012. A national increase in the laboratory-confirmed cases of pertussis has also been observed in England and Wales, with a large number of cases being reported in very young infants [Health Protection Report, 2013]. The incidence of pertussis in Spain has also gradually increased, with significant increase in 2012- 7.5/100,000 inhabitants, especially affecting infants <3 months of age who are too young to have received the primary three doses of pertussis vaccine [Sizaire, 2014]. The number of pertussis cases reported in Australia has also been increasing with nearly 40,000 cases reported in 2011 and 2012. While the rates are highest in the primary school-aged children, due to the waning of vaccine-induced immunity, the impact of the disease remains greatest in infants under one year of age [Communicable Disease Control Directorate, 2011].

Transplacental transfer of maternal antibodies is considered to provide some degree of protection to infants in the first few months of their life [Englund, 1995]. Unfortunately, low levels of the maternal antibodies and rapid decay of the antibodies in the infants often leave them at high risk for pertussis. One way to confer protection to infants is to immunise mothers late during pregnancy. This concept of "boosting" maternal levels of antibody to pertussis has been suggested as early as 1995. However, findings suggest that pre-existing high levels of pertussis antibody in infants suppress the ultimate immune response to whole-cell diphtheria, tetanus and pertussis (DTP) vaccines [Englund, 1995]. Although slightly decreased immune responses following the primary DTPa vaccination has been observed in infants whose mothers received dTpa vaccine compared to those whose mothers did not receive dTpa vaccine, the differences did not persist following the booster vaccination in infants [Hardy-Fairbanks, 2013; Gall, 2011].

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies and the epidemiological information of *Infanrix hexa.*

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

Recent studies have shown that maternal combined reduced antigen content diphtheria-tetanus-acellular pertussis (dTpa) vaccination during pregnancy results in high pertussis antibody concentrations in infants during the period between birth and the first vaccine dose.

An analysis of data from the Clinical Practice Research Datalink (a primary care database of 520 general medical practices in England) demonstrates that maternal dTpa immunisation can decrease the incidence of infant pertussis. After a maternal pertussis vaccination programme was introduced in October 2012 in response to a pertussis outbreak in England, the number of pertussis cases in infants younger than three months of age and the number of hospitalisations decreased significantly [Amirthalingam, 2014].

In 2013, the Advisory Committee on Immunization Practices (ACIP) recommended that all women should be vaccinated with dTpa vaccine during each pregnancy, regardless of the previous immunisation schedule [CDC, 2013]. Similar recommendations have been implemented in 18 countries including UK, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica, Argentina, Australia and some provinces in Spain [Joint Committee on Vaccination and Immunization (JCVI), 2012; Pharmaceutical Management Agency (PHARMAC), 2012; TAG, 2013]. The National Advisory Committee on Immunization in Canada recommends that all pregnant women following 26 weeks of pregnancy who have not received a dose of pertussis-containing vaccine in adulthood should be encouraged to receive dTpa vaccination. In special circumstances, such as an outbreak situation, all pregnant women who are of 26 weeks gestation or greater may be offered dTpa vaccination irrespective of their immunization history [Warshawsky, 2014; Public Health Agency of Canada, 2014].

All infants born to pregnant women who participated in study 116945 [DTPA (BOOSTRIX)-047] will be followed-up to study the immunogenicity and safety of ***GlaxoSmithKline*** (GSK) Biologicals' combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b vaccine (DTPa-HBV-IPV/Hib)*, Infanrix hexa,* given as primary and booster vaccination. Study 201330 [DTPA (BOOSTRIX)-048 PRI] will be conducted to assess the immunogenicity and safety of *Infanrix hexa* co-administered with *Prevenar 13* as the primary vaccination course. **(Amended 12 December 2016)**

The present study will be performed to study the immunogenicity and safety of the booster dose of *Infanrix hexa* in infants who were born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery ***and who completed their primary vaccination series as per protocol requirement in study DTPA (BOOSTRIX)-048 PRI.***. **(Amended 12 December 2016)**

1.2.2. Rationale for the study design

This phase IV study is a follow-up of the study 201330 [DTPA (BOOSTRIX)-048 PRI] where infants in both the groups received *Infanrix hexa* co-administered with *Prevenar*

13 as part of the primary vaccination ***series***. The immunogenicity and safety of *Infanrix hexa* when given as a booster dose ***according to the routine national/ local immunization schedule or as specified in the SPM*** will be evaluated. Subjects will receive *Prevenar 13* ***according to the routine national/ local immunization schedule or as specified in the SPM*** as a co-administered vaccine in this study. **(Amended 12 December 2016)**

This study will have two groups:

- 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 infants 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***. **(Amended 12 December 2016)**.
- 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 infants 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***. **(Amended 12 December 2016)**.

The study will be open-label since the treatment allocation is similar between the two groups. Also, the data related to the study groups will be unblinded at the end of study 116945 [DTPA (BOOSTRIX)-047].

Currently, the effect of *Boostrix* administered to mothers during pregnancy or immediately post-delivery on the neurodevelopment of infants is unknown. Therefore, the neurodevelopment of the subjects will be studied at 9 months and 18 months of age in this study. To assess the neurodevelopmental status, the ***investigator or designate*** will complete a standardised developmental screening tool, Ages and Stages Questionnaire-3 (ASQ-3) via a paper questionnaire ***with subjects' parent(s)/LAR(s) during the study visits or phone call*** [ASQ-3, 2016]. **(Amended 12 December 2016)**

Any subject who scores below the cut-off i.e., a score more than 2 Standard Deviations (SDs) below the mean score for the U.S. reference group (i.e., black zone in the score chart) in any of the five domains of the ASQ-3 (i.e., communication, gross motor, fine motor, problem solving, and personal-social) will be referred to a developmental specialist for formal neurodevelopmental assessment (e.g., using the Bayley Scale for Infant Development, Version III [BSID-III]) [Bayley-III, 2006]. An overall neurodevelopmental assessment in the areas of cognitive, language, motor, social-emotional and adaptive behaviour will be rendered using BSID-III. A BSID-III score more than 2 SDs below the mean score for the U.S. reference group will be considered as a neurodevelopmental impairment.

1.3. Benefit: Risk Assessment

Please refer to the current Investigator Brochure ***(IB)*** for the summary of potential risks and benefits of *Infanrix hexa.* **(Amended 12 December 2016)**

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational study vaccine *Infanrix hexa*		
Hypersensitivity including allergic reaction such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Rüggeberg, 2007].	Anaphylaxis following vaccine administration is an exclusion criterion for study participation and a contraindication to vaccination. The onset of vaccine-related allergic symptoms is typically quite prompt. In order to treat subjects with a serious allergic reaction to vaccination, all subjects will need to remain under observation (i.e., visibly followed; no specific procedure) at the vaccination centre for at least 30 minutes after vaccination.
Temperature of ≥ 40.0° C within 48 hours, not due to another identifiable cause	As outlined in the Infanrix hexa ***Reference Safety Information*** (RSI) from clinical trials and post-marketing safety data, this adverse event (AE)/serious adverse event (SAE) is recognized as well-characterized identified risks for Infanrix hexa. **(Amended 12 December 2016)**	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.
Hypotonic-hyporesponsive episode	As outlined in the *Infanrix hexa* RSI from clinical trials and post-marketing safety data, this AE/SAE is recognized as well-characterized identified risks for *Infanrix hexa*.	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.
Convulsions	As outlined in the *Infanrix hexa* RSI from clinical trials and post-marketing safety data, this AE/SAE is recognized as well-characterized identified risks for *Infanrix hexa*.	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.
Encephalopathy	As outlined in the *Infanrix hexa* RSI from clinical trials and post-marketing safety data, this AE/SAE is recognized as potential risk for *Infanrix hexa*.	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.
Study Procedures		
Not applicable.		
Other *(Prevenar 13)*		
Hypersensitivity including allergic reaction such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine	Anaphylaxis following vaccine administration is an exclusion criterion for study participation and a

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
	administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Rüggeberg, 2007].	contraindication to vaccination. The onset of vaccine-related allergic symptoms is typically quite prompt. In order to treat subjects with a serious allergic reaction to vaccination, all subjects will need to remain under observation (i.e., visibly followed; no specific procedure) at the vaccination centre for at least 30 minutes after vaccination.
Temperature of ≥ 40.0° C within 48 hours, not due to another identifiable cause	As outlined in *Prevenar 13* European public assessment report (EPAR), increased fever rates were observed when *Prevenar 13* was co-administered with *Infanrix hexa*.	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator. **(Amended 12 December 2016)**
Hypotonic-hyporesponsive episode	As outlined in the *Prevenar 13* summary of product characteristics (SPC), this AE/SAE is recognized as well-characterized identified risks for *Prevenar 13*.	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.
Convulsions	As outlined in the *Prevenar 13* SPC, this AE/SAE is recognized as well-characterized identified risks for *Prevenar 13*.	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.

1.3.2. Benefit Assessment

Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b (Hib) are common causes of diseases in children worldwide, with significant morbidity and mortality. A dramatic decline in the incidence of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Hib has been evidenced in countries in which infants are routinely immunised against these diseases. By receiving the *Infanrix hexa* vaccine, the subjects may be protected against the above mentioned diseases. In addition, the subjects will undergo a physical examination at Visit 2 before booster vaccination. In case the study doctor discovers any medical condition, the subject will be referred to the local healthcare system. The vaccine and study related tests will be provided free of cost to the subjects. **(Amended 12 December 2016)**

1.3.3. Overall Benefit: Risk Conclusion

The benefit/risk profile of *Infanrix hexa* for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b continues to be favourable.

2. OBJECTIVES

2.1. 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 10.1 for the definition of the primary endpoint.

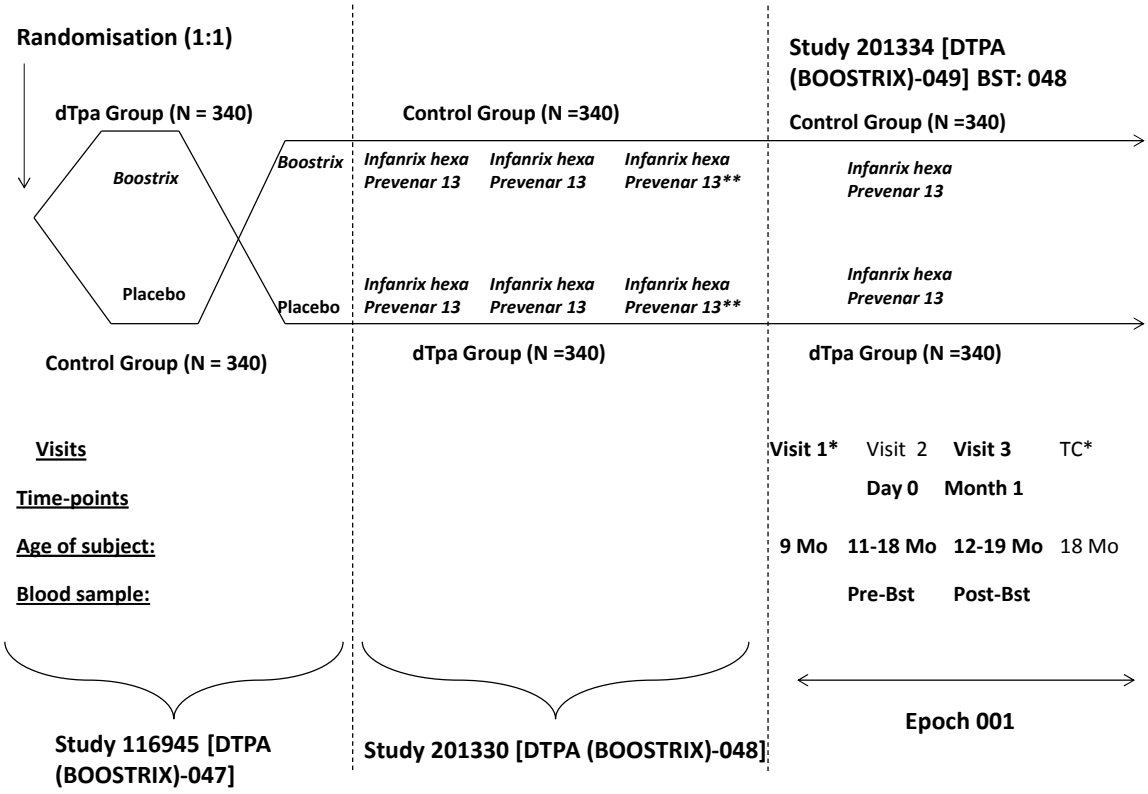
2.2. Secondary objectives

- 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.

Refer to Section 10.2 for the definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW

(Amended 12 December 2016)



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 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), 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.**(Amended 12 December 2016)**

- ***End of Study (EoS): Last testing results released of samples collected at Visit 3.*** **(Amended 12 December 2016)**
- 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***. **(Amended 12 December 2016)**.

  – 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***. **(Amended 12 December 2016)**.

Table 1 Study groups and epoch foreseen in the study

(Amended 12 December 2016)

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

(Amended 12 December 2016)

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***. **(Amended 12 December 2016)**

- 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]. **(Amended 12 December 2016)**

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***. **(Amended 12 December 2016)**.

4. STUDY COHORT

4.1. Number of subjects/centres

A maximum of 680 infants aged 9 months will be enrolled in this study. Blood samples will be taken from all subjects in order to evaluate the immunogenicity endpoints. The tracking of recruitment of subjects into the study will be performed using SBIR.

Overview of the recruitment plan:

- Enrolment will be offered to all eligible infants born to mothers from the 116945 [DTPA (BOOSTRIX)-047] study ***and having completed their primary vaccination series as per protocol requirement in study 201330 [DTPA (BOOSTRIX)-048 PRI]***. **(Amended 12 December 2016)**
- The study will be monitored by a local Study Monitor.
- The treatment allocation and confirmation of the enrolment of subjects into the study will be tracked using SBIR.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects' parent(s)/LAR(s) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
- A male or female child 9 months of age at the time of enrolment.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- 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]***. **(Amended 12 December 2016)**

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Child in care
  Please refer to the glossary of terms for the definition of child in care.

- 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).

- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period within six months prior to the booster vaccine dose. For corticosteroids, this will mean prednisone ≥0.5mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
- 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.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Major congenital defects.
- Serious chronic illness.
- 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.
- Encephalopathy defined as an acute, severe central nervous system disorder occurring within seven days following vaccination with *Infanrix hexa* and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.
- History of Hib, diphtheria, tetanus, pertussis, pneumococcal, poliovirus and hepatitis B diseases since the conclusion visit of study 201330 [DTPA (BOOSTRIX)-048 PRI].
- 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].
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines (e.g.: antigen, excipients).
- Hypersensitivity to latex.
- History of any neurological disorders or seizures.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F on rectal route.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ***International Conference on Harmonization*** (ICH) Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.
(Amended 12 December 2016)

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject's parent(s)/LAR(s) informed consent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/thumb printed informed consent must be obtained from each subject's parent(s)/LAR(s), as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification

Subjects will retain the same subject number as their mothers in the 116945 [DTPA (BOOSTRIX)-047] study ***and their own subject number in study 201330 [DTPA (BOOSTRIX)-048 PRI]***. These subject numbers will also be used to identify blood samples collected in the study. **(Amended 12 December 2016)**

5.2.2. Randomisation of treatment

5.2.2.1. Treatment allocation to the subject

There will be no randomisation of subjects into groups in this study. The infants enrolled in this study will be allocated to the same groups as their mothers in the 116945 [DTPA (BOOSTRIX)-047] study ***and as themselves in study 201330 [DTPA (BOOSTRIX)-048 PRI]***. Subjects will retain the same subject number as their corresponding mothers from the 116945 [DTPA (BOOSTRIX)-047] study. **(Amended 12 December 2016)**

The treatment numbers will be allocated by dose.

5.2.2.1.1. Study group and treatment number allocation

The target will be to enrol maximum of 680 eligible subjects aged 9 months (approximately 340 subjects in each group).

After obtaining the signed and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, ***investigator or designate will complete a standardised developmental screening tool, Ages and Stages Questionnaire-3 via a paper questionnaire (at Visit 1) with*** subjects' parent(s)/LAR(s). At Visit 2, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will provide the treatment number to be used for ***vaccination***. **(Amended 12 December 2016)**

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.3. Method of blinding

This study will be conducted in an open-label manner since the treatment allocation is similar between the two groups. Also, the data related to the study groups will be unblinded at the end of study 116945 [DTPA (BOOSTRIX)-047].

Note: The study personnel operating SBIR and the site staff will remain blinded towards the treatment allocation ***of the mother in study 116945 [DTPA (BOOSTRIX)-047]*** until the completion and unblinding of study 116945 [DTPA (BOOSTRIX)-047] to prevent the potential unblinding of the treatment allocation to the mother in 116945 [DTPA (BOOSTRIX)-047]. **(Amended 12 December 2016)**

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects**.**

5.4.1. Independent Data Monitoring Committee

An IDMC will oversee the safety of infants born to mothers who were vaccinated with *Boostrix* during pregnancy or immediately post-delivery in the clinical study 116945 [DTPA (BOOSTRIX)-047], infants who received primary vaccination series of *Infanrix hexa* and *Prevenar13* ***as per protocol requirement*** in the study 201330 [DTPA (BOOSTRIX)-048 PRI] and booster vaccination in 201334 [DTPA (BOOSTRIX)-049 BST: 048] study.

To facilitate the review, the IDMC will be provided with all relevant safety data including data on each SAE, grade 3 local and general solicited AEs, unsolicited AEs and neurodevelopmental status of infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery at specified times and access to data on request by an unblinded statistician. The frequency of the meeting will be ***documented in the IDMC charter*** **(Amended 12 December 2016)**

The operating rules of the IDMC ***are*** documented in a charter.

5.4.2. Responsibilities

(Amended 12 December 2016)

The overall responsibility of the IDMC is to protect the ethical and safety interests of ***subjects*** recruited into this study while protecting as far as possible the scientific validity of the data.

The details of the IDMC's responsibilities and conduct of meetings will be provided in the IDMC ***c***harter. The IDMC charter will also clearly state who will conduct the statistical analysis (ICH E9). Key responsibilities of the IDMC are the following:

- Prior to study start, the IDMC will review the protocol with special attention to safety monitoring procedures and will make recommendations for adjustments, if required.
- ***The IDMC will be informed of any amendment to the initial protocol***
- The IDMC will review the ***unblinded*** safety data from the study (i.e., each SAE, grade 3 local and general solicited AEs , unsolicited AEs ***and neurodevelopmental status***), provide GSK Biologicals with indications on safety profiles and make recommendations on further study conduct.
- The IDMC will review the final analysis provided by the sponsor.

5.4.3. Composition of the IDMC

(Amended 12 December 2016)

IDMC members will not participate in the study, neither as principal or co-investigators nor as study ***subject*** care physicians. They can also not provide medical care to a ***subject*** enrolled in the study. The IDMC will include medically qualified experts in the field under study (paediatrician and a biostatistician). The person specifically selected to chair the IDMC will be required not only to have appropriate training for the study but also to have experience serving on one or more IDMCs. The IDMC also may convene an ad-hoc meeting should it deem necessary for review of specific cases/safety concerns.

Neither the IDMC chair, nor the members are allowed to communicate with the investigators involved in the trial about data from the study. If needed, additional information should be obtained from the sponsor. The sponsor should inform the investigators in case of any safety concerns observed by the IDMC.

5.4.4. GSK Biologicals' safety review team

(Amended 12 December 2016)

A***t GSK Biologicals, a*** Safety Review Team ***(SRT) will include*** the Central Safety Physician ***and Safety Scientist***, the ***Clinical Research and development Lead (***CRDL) and Biostatistician of the project as well as Epidemiology and Regulatory representatives***.*** ***The SRT*** will be responsible for reviewing the ***blinded*** safety data related to the investigational product in this study and due to *Boostrix* vaccine received by the mother in 116945 [DTPA (BOOSTRIX)-047] study***. The SRT review will be done*** on a regular basis to identify any potential safety issues or signals in order to evaluate and agree on action plans, if necessary.

The IDMC will provide recommendation to the sponsor ***which will be shared with the investigators***.

5.5. Outline of study procedures

The list of study procedures is detailed in Table 4.

Table 4 List of study procedures

(Amended 12 December 2016)

Age	9 months	*11*-18 months	*12*-19 months	18 months **
Epoch		**Epoch 001**		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Phone contact ***
Time points	***Months -2 to -9***	***Day 0*** **	***Month 1*** **	**Day 0 to Month7 ****
Sampling time points		**Pre-Bst**	**Post-Bst**	
Informed consent	●			
Check inclusion/exclusion criteria	●			
Collect demographic data		●		
Medical history, including medication/vaccine history §	●	●		
Physical examination		***O***		
Check contraindications and warnings and precautions		O		
Pre-vaccination body temperature		●		
Measure/record length, weight and head circumference		●		
Vaccine				
Treatment number allocation		O		
Recording of administered treatment number		●		
Vaccine administration		●		
Laboratory assays				
Blood sampling for antibody determination (approx 5 mL)		●	●	
Safety assessments				
Record any concomitant medication/vaccination		●	●	
Record any intercurrent medical conditions			●	
Distribution of diary cards		●		
Recording of solicited adverse events (Day 0-Day 3) ***post-vaccination*** by subjects' parent(s)/LAR(s) in the diary card		●		
Recording of non-serious adverse events within 31 days (Day 0-Day 30) post-vaccination, by subjects' parent(s)/LAR(s) in the diary card		●	●	
Recording of large injection-site reactions		●		
Return of diary cards			O	
Diary card transcription by investigator or site staff			●	
Recording of neurodevelopmental status by the subjects' parent(s)/LAR(s) in the ASQ-3 paper questionnaire	●	● **	● **	● **
Transcribe the information in ASQ-3 paper questionnaire, by the investigator	●	● **	● **	● **
Recording of SAEs and AEs/SAEs leading to withdrawal	●	●	●	● **
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●
Study Conclusion †				●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
* ***For Czech Republic, the phone call at 18 months may be replaced by a clinic visit if deemed preferable by the study team.***

** The neurodevelopmental status will be recorded when the subject is 9 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. If the subject is referred to a developmental specialist for formal assessment, then this information needs to be recorded in the eCRF. Also, the overall assessment of delay by the specialist should be recorded in the eCRF.
§ History of all medications given to the infants after the end of 201330 [DTPA (BOOSTRIX)-048 PRI] until enrolment in this study will be recorded in the eCRF ***at Visit 1 and updated at Visit 2 for all new information***
† Study conclusion will be at Visit 3 or after ASQ-3 is completed at 18 months of age.
Pre-Bst: Blood sample to be collected before the booster dose.
Post-Bst: Blood sample to be collected one month after the booster dose.

The intervals between study visits are presented in Table 5.

Table 5 Intervals between study visits

(Amended 12 December 2016)

Interval	Optimal length of interval [1]	Allowed interval [2]
Birth→Visit 1	9 months old	9 months old +30 days *
Visit 1→Visit 2	***2-10*** months **	***2-10*** months **
Visit 2 → Visit 3	30 days **	21-48 days **
Phone contact	18 months old	18 months old ± 30 days *

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects will not be eligible for inclusion in the ATP cohort for analysis of immunogenicity if they make the study visit outside this interval.
* ***The allowed interval for Visit 1 and Phone contact is calculated depending on the official recommendation for age for completion of the ASQ-3 questionnaire (9 months and 0 days through 9 months and 30 days and 17 months and 0 days through 18 months of age and 30 days).*** In case subjects who were born prematurely by three or more weeks are enrolled, prematurity adjustment needs to be performed for the 9th and 18th month ASQ-3 questionnaire completion. Refer to Section 5.6.2.13 and SPM for more details.
** ***The intervals required in the table are the minimum and maximum intervals for the study and the allowed intervals for inclusion in the ATP cohort will correspond to approximately 30 days before or after the time window corresponding to the national/ local immunization schedule or as specified in the SPM***
If subjects return for the ***Visit 3*** prior to 30 days, the parent(s)/LAR(s) should take home the diary card and continue to record unsolicited safety information until 30 days post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects' parent(s)/LAR(s) who have not mailed/sent them in.

5.6. Detailed description of study procedures

5.6.1. Procedures prior to study participation

5.6.1.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate.

At the end of the primary vaccination series study, 201330 [DTPA (BOOSTRIX)-048 PRI], parent(s)/LAR(s) will be informed about this booster follow-up study [DTPA (BOOSTRIX)-049 BST: 048] in which their infants will receive a booster dose of the study vaccines. When the subject is approximately 9 months of age, the ***investigator or designee*** will complete a standardised developmental screening tool, Ages and Stages

Questionnaire-3 (ASQ-3) via a paper questionnaire ***with subjects' parent(s)/LAR(s) during the*** Visit 1. **(Amended 12 December 2016)**

5.6.2. Procedures during study participation

5.6.2.1. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.2.2. Collect demographic data

Record demographic data such as ***the full date of birth*** in the subject's eCRF at Visit 2. **(Amended 12 December 2016)**

5.6.2.3. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record ***in the eCRF*** any pre-existing conditions or signs and/or symptoms present in a subject at Visit 1 ***and update with all new information at Visit*** 2.

All events that occur after the end of primary study 201330 [DTPA (BOOSTRIX)-048 PRI] until enrolment in 201334 [DTPA (BOOSTRIX)-049 BST: 048] study will be recorded as part of the subject's medical history.

5.6.2.4. Medication and vaccination history

Obtain the subject's medication and vaccination history by interview and/or review of the subject's medical records and record ***in the eCRF*** any medication and vaccine administration at Visits 1 and ***update with all new information at Visit*** 2.

5.6.2.5. Physical examination

(Amended 12 December 2016)

Perform a physical examination (***including vital signs)*** prior to vaccination (Visit 2). ***The extent of the physical examination to be performed are as per investigator or delegate discretion to determine if the subject is healthy.***

If ***it is determined*** that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.2.6. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the vaccination visit (Visit 2). Refer to Sections 6.5 and 6.6 for more details.

5.6.2.7. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccines administration. The preferred route for recording temperature in this study will be axillary/rectal. If the subject has fever [fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 5).

5.6.2.8. Record body length, weight and head circumference (Amended 12 December 2016)

Record body weight (kg), height (cm) and head circumference (cm) of the subject at Visit 2 in the eCRF.

5.6.2.9. Treatment number allocation

Treatment number allocation will be performed at Visit 2 as described in Section 5.2.2. The number of administered treatment must be recorded in the eCRF.

5.6.2.10. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.2.10.1. Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.7.2:

- 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.
- After centrifugation, serum samples should be kept at –20°C/–4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.2.11. Study Vaccines administration

- After completing all prerequisite procedures prior to vaccination, a booster dose of study vaccines will be administered intramuscularly (IM) ***either*** in the thigh ***or in the deltoid, according to the national recommendation /local practice*** (refer to Section 6.3 for detailed description of the vaccines administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccines administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5). **(Amended 12 December 2016)**

- The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.2.12. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.8.

5.6.2.13. Assessment of neurodevelopmental status

The parent(s)/LAR(s) will be asked to complete a standardised developmental screening tool known as ASQ-3 when the subject is 9 months and 18 months old [ASQ-3, 2016]. The ASQ-3 has been used globally and translated into different languages. The tool has been demonstrated to reliably and accurately identify children with delays who should receive further in-depth assessment. The ASQ-3 includes a series of questions designed to assess five areas of development: communication, gross motor, fine motor, problem solving, and personal-social. The questions target behaviours that are appropriate for particular developmental status. These behaviours are easy for the parent(s)/LAR(s) to observe and they are asked to indicate whether or not the subject can perform the behaviour. The ASQ-3 will be completed by the ***investigator or designee with*** the parent(s)/LAR(s) ***during the study visits or phone call*** when the subject is 9 and 18 months of age, via a paper questionnaire *. These time- points comply with the recommended developmental screening assessment guidelines from the American Academy of Pediatrics [Council on Children with Disabilities, 2006]. ***The investigator or designee may discuss the results with the parents if deemed necessary.*** **(Amended 12 December 2016)**

The ASQ-3 has narrow age intervals ***(9 months and 0 days through 9 months and 30 days and 17 months and 0 days through 18 months of age and 30 days)***, so age must be calculated to the month and day from the date the ASQ-3 will be completed. **(Amended 12 December 2016)**

If a baby was born three or more weeks prematurely, the number of weeks premature should be subtracted from the child's actual age [ASQ, 2014]. Refer to the SPM for more details and examples.

Any subject who scores below the cut-off i.e., a score more than 2 Standard Deviations (SDs) below the mean score for the U.S. reference group (i.e., black zone in the score chart) in any of the five domains of the ASQ-3 (i.e., communication, gross motor, fine motor, problem solving, and personal-social) will be referred to a developmental specialist for formal neurodevelopmental assessment (e.g., using the Bayley Scale for Infant Development, Version III [BSID-III]) [Bayley-III, 2006]. An overall neurodevelopmental assessment in the areas of cognitive, language, motor, social-emotional and adaptive behaviour will be rendered using BSID-III. A BSID-III score

more than 2 SDs below the mean score for the U.S. reference group will be considered as a neurodevelopmental impairment. If the subject is referred to a developmental specialist for formal assessment then this information should be recorded in the eCRF. Also, the overall assessment of delay by the specialist should be recorded in the eCRF.

*Note: It is encouraged that the parent(s)/LAR(s) of the subject complete the ASQ-3 during their visit to the study centre at Visit 2 or Visit 3. In case the subject completes Visit 3 before 18 months of age, the study staff will contact the parents/LAR(s) via phone to 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.*** **(Amended 12 December 2016)**

5.6.2.14. Recording of AEs and SAEs

- Refer to Section 8.2 for procedures for the investigator to record AEs and SAEs. Refer to Section 8.3 for guidelines and how to report SAE reports to GSK Biologicals.
- The subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.
- Record large injection site reactions as described in 8.1.3.1.
- At the vaccination visit (Visit 2), diary cards will be provided to the subject's parent(s)/LAR(s). The subject's parent(s)/LAR(s) will record body (axillary/rectal) temperature and any solicited local/general AEs (i.e., on the day of vaccination and during the next three days) or any unsolicited AEs (i.e., on the day of vaccination and during the next 30 days) occurring after vaccination. The subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at the next study visit.
- Collect and verify completed diary cards during discussion with the subject's parent(s)/LAR(s) at Visit 3.
- Any unreturned diary cards will be sought from the subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure. The investigator/ ***designee*** will transcribe the collected information into the eCRF in English. **(Amended 12 December 2016)**

5.6.2.15. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness,
- complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

Please refer to the SPM ***and laboratory manual*** for details on biospecimen management (handling, storage and shipment). **(Amended 12 December 2016)**

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed, will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject's parent(s)/LAR(s).

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ***According-to-Protocol (***ATP) analysis (See Section 10.4 for the definition of cohorts to be analysed). The investigator must ensure that

his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM. **(Amended 12 December 2016)**

5.7.2. Biological samples

The biological sample to be collected, quantity and time point of collection are mentioned in Table 6.

Table 6 Biological samples

Sample type	Quantity	Unit	Time points
Blood	Approximately 5	ml	Visit 2 and Visit 3

5.7.3. Laboratory assays

Please refer to APPENDIX A for the address of the clinical laboratories used for sample analysis.

Serological assays for the determination of antibodies will be performed at a GSK Biologicals' laboratory or in a laboratory designated by GSK Biologicals using standardised and validated procedures (refer to Table 7).

Table 7 Humoral Immunity (Antibody determination)

(Amended 12 December 2016)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off***	Laboratory †
SER	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	NA	IU/ml	***0***.1	GSK Biologicals*
SER	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	NA	IU/ml	***0***.1	GSK Biologicals*
SER	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals*
SER	Bordetella pertussis.Pertactin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals*
SER	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals*
SER	Hepatitis B Virus.Surface Ab	CLIA	ADVIA Centaur anti-HBs2 (Siemens Healthcare)	mIU/ml	6.2	GSK Biologicals*
SER	Poliovirus Sabin Type 1 Ab	NEU	NA	ED50	8	GSK Biologicals*
SER	Poliovirus Sabin Type 2 Ab	NEU	NA	ED50	8	GSK Biologicals*
SER	Poliovirus Sabin Type 3 Ab	NEU	NA	ED50	8	GSK

System	Component	Method	Kit / Manufacturer	Unit	Cut-off***	Laboratory †
						Biologicals*
SER	Haemophilus influenzae type b.Polyribosyl Ribitol Phosphate Ab	ELI	NA	µg/ml	***0***.15	GSK Biologicals*
SER	Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG Streptococcus pneumoniae.Polysaccharide 03 Ab.IgG Streptococcus pneumoniae.Polysaccharide 05 Ab.IgG Streptococcus pneumoniae.Polysaccharide 06A Ab.IgG Streptococcus pneumoniae.Polysaccharide 06B Ab.IgG Streptococcus pneumoniae.Polysaccharide 07F Ab.IgG Streptococcus pneumoniae.Polysaccharide 09V Ab.IgG Streptococcus pneumoniae.Polysaccharide 14 Ab.IgG Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG Streptococcus pneumoniae.Polysaccharide 19A Ab.IgG Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG	ELIF or multiplex	NA	µg/ml	***0***.05 or equivalent cut-off for the multiplex	GSK Biologicals*

System	Component	Method	Kit / Manufacturer	Unit	Cut-off***	Laboratory †
SER	Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG Streptococcus pneumoniae.Polysaccharide 03 Ab.IgG Streptococcus pneumoniae.Polysaccharide 04 Ab.IgG Streptococcus pneumoniae.Polysaccharide 05 Ab.IgG Streptococcus pneumoniae.Polysaccharide 06A Ab.IgG Streptococcus pneumoniae.Polysaccharide 06B Ab.IgG Streptococcus pneumoniae.Polysaccharide 07F Ab.IgG Streptococcus pneumoniae.Polysaccharide 09V Ab.IgG Streptococcus pneumoniae.Polysaccharide 14 Ab.IgG Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG Streptococcus pneumoniae.Polysaccharide 19A Ab.IgG Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG	ELI	NA	µg/ml	***0***.15	WHO reference laboratory**

*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Neomed Lab Inc, Canada.
** At the discretion of GSK Biologicals, pneumococcal testing may be done at a GSK Biologicals laboratory or the WHO reference laboratory
****** Assay cut-off and unit might be subject to change during the course of the study (e.g. in case of requalification, revalidation or standardization). In this case, this will be documented in the clinical report.***
† Refer to the APPENDIX A for the laboratory addresses.
SER = Serum
ELI = Enzyme-linked immunosorbent assay (ELISA)
ELIF = 22F Inhibition ELISA
NEU = Neutralisation assay
CLIA = ChemiLuminescence ImmunoAssay
IU/mL = International Units/millilitre
mIU/mL = milliInternational Units/millilitre
EL.U/mL = ELISA Units/millilitre
µg/ml = Micrograms/millilitre

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

The immunological read-outs are presented in Table 8.

Table 8 Immunological read-outs

(Amended 12 December 2016)

Blood sampling time point		No. subjects	Component	Components priority rank
Type of contact and time point	Sampling time point			
Visit 2 (***Day 0)***	Pre-Bst	All	PT, FHA, PRN D, T HBs, PRP Poliovirus types 1, 2, 3 13 pneumococcal serotypes	1 2 3 4 5
Visit 3 (***Day 30***)	Post-Bst	All	PT, FHA, PRN HBs, PRP D, T Poliovirus types 1, 2, 3 13 pneumococcal serotypes	1 2 3 4 5

Pre-Bst: Blood sample to be collected before the booster dose.
Post-Bst: Blood sample to be collected one month after the booster dose

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 8.

5.7.5. Immunological correlates of protection

The following cut-offs are accepted as immunological correlates of protection:

- Specific antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus) will be measured by Enzyme-linked immunosorbent assay (ELISA), for which the threshold of 0.1 International Units per ml (IU/ml) provides a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983].
- Antibodies against the hepatitis B surface antigen (anti-HBs) will be measured using ChemiLuminescence ImmunoAssay (CLIA). The cut-off of the test is set at 6.2 mIU/ml. An antibody concentration ≥ 10 mIU/ml defines seroprotection [CDC, 1991].
- Antibodies against poliovirus types 1, 2 and 3 will be determined by a virus micro-neutralisation test adapted from the World Health Organization Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis [WHO, 1993]. Titres will be

expressed in terms of the reciprocal of the dilution resulting in 50% inhibition. Samples with a titre greater than or equal to 1:8 will be considered as seropositive and protective.

- Data from subjects given unconjugated Hib vaccine suggest that, in the absence of induction of immunological memory, a concentration of 0.15 μg/mL is indicative of short-term protection, with 1 μg/mL considered indicative of long-term protection [Käyhty, 1983; Anderson, 1984].
- No serological correlate of protection against pertussis has been established [Plotkin, 2010]. Antibodies against the pertussis components pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) will be measured by ELISA. The seropositivity cut-off for all three pertussis antibodies in ELISA is 5 EL.U/ml. Subjects with antibody concentration below the cut-off will be considered seronegative.
- Pneumococcal serotype specific total immunoglobulin G (IgG) antibodies (antibodies to 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) will be each measured by 22F-inhibition ELISA [Concepcion, 2001] or multiplex. The antibody concentration for ELISA will be determined by logistic log comparison of the ELISA curves with a standard reference serum 89-SF available from the US Food and Drug Administration for which concentration of IgG and IgM to the serotypes are known in μg/ml [Quataert, 1995]. The cut-off for ELISA is 0.05 μg/ml. No correlate of protection is defined for the immune response to pneumococcal antigens. At the discretion of GSK Biologicals, this assay will be performed either at a GSK laboratory or at the WHO reference laboratory. The assay cut-off of the 22F-inhibition ELISA test performed at the WHO reference laboratory is 0.15 μg/ml.

The immunological assay results will be communicated to the investigator as soon as they become available.

The investigator is encouraged to share the immunological assay results for non-responders with the study subjects' parent(s)/LAR(s).

For the subjects identified as non-responders, it remains the responsibility of the investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

6. STUDY VACCINES AND ADMINISTRATION

6.1. Description of study vaccines

The candidate vaccine to be used has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g., release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

The study vaccines, formulation and presentation is detailed in Table 9.

Table 9 Study vaccines

Treatment name	Vaccines name	Formulation	Presentation	Volume to be administered*	Number of doses
Infanrix hexa	DTPa-HBV-IPV	DT>=30IU; TT>=40IU; PT=25µg; FHA=25µg; PRN=8µg; HBsAg=10µg; Inactivated Poliovirus type 1 (Mahoney strain)=40DU; Inactivated Poliovirus type 2 (MEF-1 strain)=8DU; Inactivated Poliovirus type 3 (Saukett strain); Aluminium=700µg Al3+	The DTPa-HBV-IPV component is presented as a turbid white suspension in a pre-filled syringe.	0.5 ml *	1
	Hib	PRP=10µg; TT~=25µg Aluminium as salts = 0.12 mg	The lyophilised Hib component is presented as a white pellet in a glass vial; it must be reconstituted before use with the liquid DTPa-HBV-IPV component.		
Prevenar 13	Prevenar 13	PS1=2.2µg CRM197; PS3=2.2µg CRM197; PS4=2.2µg CRM197; PS5=2.2µg CRM197; PS6A=2.2µg CRM197; PS6B=4.4µg CRM197; PS7F=2.2µg CRM197; PS9V=2.2µg CRM197; PS14=2.2µg CRM197; PS18C=2.2µg CRM197; PS19A=2.2µg CRM197; PS19F=2.2µg CRM197; PS23F=2.2µg CRM197; $AlPO_4$=125µg Al3+	Suspension for injection in a pre-filled syringe	0.5 ml	1

*After reconstitution

6.2. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorised study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccines.

6.3. Dosage and administration of study vaccines

The dosage and administration of study vaccines is given in Table 10.

Table 10 Dosage and administration

(Amended 12 December 2016)

Type of contact and time point	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side [3]
Visit 2 (***Day 0)***	0.5 mL	dTpa Group and Control Group	*Infanrix hexa*	IM	***Thigh or Deltoid*** [2]	R
Visit ***3*** (***Day 30)***	0.5 mL	dTpa Group and Control Group	*Prevenar 13*	IM	***Thigh or Deltoid*** [2]	L

[1]Intramuscular (IM)
[2] The vaccines should be administered in the thigh or deltoid, according to the national recommendations /local practice
[3]Right (R), Left (L)

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 10% additional vaccine doses will be supplied to replace those that are unusable.

6.5. Contraindications to vaccination

Since this is a booster study (single dose), contraindications have been included as part of the exclusion criteria.

The following events constitute contraindications to administration of *Infanrix hexa* at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.4).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be axillary/rectal.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines/products.

6.6. Warnings and precautions

The information below presents, in addition to the contraindications in Section 6.5, warnings and precautions to administration of *Infanrix hexa.*

- As with other vaccines, administration of *Infanrix hexa* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contraindication.
- Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.
- If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:
  - Temperature of ≥ 40.0°C within 48 hours, not due to another identifiable cause.
  - Collapse or shock-like state (hypotonic-hyporesponsiveness episode ***[HHE]***) within 48 hours of vaccination. **(Amended 12 December 2016)**
  - Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
  - Convulsions with or without fever, occurring within three days of vaccination.

- As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.
- *Infanrix hexa* should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.
- In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.
- Do not administer the vaccine intravascularly or intradermally.
- A protective immune response may not be elicited in all vaccinees.
- A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of *Infanrix hexa*. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.
- Since the Hib capsular polysaccharide antigen is excreted in the urine, a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.
- Data from clinical studies indicate that, when *Infanrix hexa* is co-administered with pneumococcal conjugate vaccine, the rate of febrile reactions is higher compared to that occurring following the administration of *Infanrix hexa* alone.
- Increased reporting rates of convulsions (with or without fever) and HHE were observed with concomitant administration of *Infanrix hexa* and *Prevenar 13.* **(Amended 12 December 2016)**

Warnings and Precautions for the use of *Prevenar13:*

- *Prevenar 13* must not be administered intravascularly.
- As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.
- *Prevenar13* should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.
- *Prevenar 13* will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine, and will not protect against other microorganisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, *Prevenar 13* may not protect all individuals receiving the vaccine from pneumococcal disease.
- Individuals with impaired immune responsiveness, whether due to the use of immuno-suppressive therapy, a genetic defect, human immunodeficiency virus

(HIV) infection, or other causes, may have reduced antibody response to active immunisation.

- Increased reporting rates of convulsions (with or without fever) and HHE were observed with concomitant administration of *Infanrix hexa* and *Prevenar 13*. **(Amended 12 December 2016)**

Refer to the latest approved product label/package insert for warnings and precautions for the use of *Infanrix hexa* and *Prevenar 13*.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator should question the subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject.

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period starting from the administration of the dose of study vaccines (Visit 2) and ending at Visit 3 ***(Day 0 to Day 30)***
- Any concomitant vaccination administered in the period starting from the administration of the dose of study vaccines (Visit 2) and ending at the study visit ***3 (Day 0 to Day 30)***.

  Note: Medications/vaccinations listed prior to the dose of study vaccine are to be recorded as medical/vaccination history.
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g., an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route]**.**
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol or administered at any time during the study period for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.

6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.4 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used within 30 days preceding the dose of study vaccine, or planned use during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g., infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting from 30 days before each dose of vaccine and ending 30 days after*, with the exception of inactivated influenza vaccine and other vaccines given as a part of the national 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 PI and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period.

6.8. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses

At each study visit subsequent to the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

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 or are confirmed to have an alteration of their initial immune status (e.g., any confirmed or suspected immunosuppressive or immunodeficient condition).

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF**.**

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other

outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 11 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

N.B. If parent(s)/LAR(s) of infants observe 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)], they will be asked to contact the study personnel and bring the subject for an evaluation by the investigator as soon as possible. The investigator will record detailed information describing the AE on a specific large swelling reaction sheet in the eCRF.

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 12 Solicited general adverse events

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., vital signs) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present

or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2. Detecting and recording adverse events and serious adverse events

8.2.1. Time period for detecting and recording adverse events and serious adverse events

All AEs starting within 30 days following administration of the dose of study vaccines (Day 0 to Day 30) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the receipt of study vaccines and will end ***when the subject is discharged from the study.*** See Section 8.3 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time ***the subjects have been enrolled in the study***.

(Amended 12 December 2016)

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e., protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject's parent(s)/LAR(s) consents to their child/wards participation in the study until she/he is discharged from the study.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 13.

Table 13 Reporting periods for collecting safety information

(Amended 12 December 2016)

Event	V 1	V2	4 d post V2	31 d post-V2	V3	Phone contact * Study Conclusion
Age of subject	**9 months**	**_11_-18 months**			**_12_-19 months**	**18 months¶**
Timepoint	***Month -9 to -2***	***Day 0***	***Day 3***	***Day 30***	***Day 30***	***Day 0 to Month 7***
Solicited local and general AEs						
Large injection site reactions						
Unsolicited AEs						
Neurodevelopmental status¶						
AEs/SAEs leading to withdrawal from the study						
SAEs						
SAEs related to study participation or concurrent GSK medication/vaccine						

Pre-V: pre-vaccination; V: Visit; Post-V: post-visit; D: Day, M: Month;

**** For Czech Republic, the phone call at 18 months may be replaced by a clinic visit if deemed preferable by the study team.*** **(Amended 12 December 2016)**

¶ Neurodevelopmental status will be recorded at 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.
If the subject is referred to a developmental specialist for formal assessment, then this information needs to be recorded in the eCRF. Also, the overall assessment of delay by the specialist should be recorded in the eCRF.

8.2.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 13. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine the investigator will promptly notify the Study Contact for Reporting SAEs.

8.2.3. Evaluation of adverse events and serious adverse events

8.2.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccines or since the last visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.2.3.2. Assessment of adverse events

8.2.3.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 14 Intensity scales for solicited symptoms

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

*Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be axillary/rectal.

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

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

The maximum intensity of fever ***(oral, axillary or typmpanic route)*** will be scored at GSK Biologicals as follows: **(Amended 12 December 2016)**

0 = < 37.5°C
1 = ≥ 37.5°C to ≤ 38.0°C
2 = > 38.0°C to ≤ 39.0°C
3 = > 39.0°C

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.2.3.2.2. Assessment of causality

The definitions for 'NO' and 'YES' have been written in such a way that all events that have been attributed a 'NO' can be pooled with events which in the primary vaccination study were determined to be 'not related' or 'unlikely to be related' to vaccination. Those events that are attributed a 'YES' can be pooled with those events that in the past were determined to have a 'suspected' or 'probable' relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the IB and/or ***PI*** for marketed products to determine his/her assessment. **(Amended 12 December 2016)**

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines/products, it may not be possible to determine the causal relationship of general AEs to the individual vaccine

administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational vaccine?

YES	:	There is a reasonable possibility that the vaccines contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccines. There are other, more likely causes and administration of the study vaccines is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

8.2.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.2.3.4. Assessment of neurodevelopmental status

The parent(s)/LAR(s) will be asked to complete a standardised developmental screening tool known as ASQ-3. Refer to Section 5.6.2.13 for more details.

8.2.3.5. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.3. Reporting of serious adverse events

8.3.1. Prompt reporting of serious adverse events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a SAE.

Table 15 Timeframes for submitting serious adverse event reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.2. Contact information for reporting serious adverse events

Study Contact for Reporting SAEs
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Fax: PPD or PPD Email address: PPD

8.3.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does

not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.3.4. Updating of SAE information after removal of write access to the subject's eCRF

When additional SAE information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

8.3.5. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.3.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.4. Follow-up of adverse events and serious adverse events

8.4.1. Follow-up of adverse events and serious adverse events

8.4.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 15).

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visit/contact until 30 days after the vaccination.

8.4.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using electronic Expedited Adverse Events Report.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 6.7).

8.6. Subject card

Study subjects' parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject's parent(s)/LAR(s). In an emergency situation this card serves to inform the responsible

attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects' parent(s)/LAR(s) must be instructed to keep subject cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject's parent(s)/LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.4.1.2).

10. STATISTICAL METHODS

10.1. 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.

10.2. 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.

10.3. Determination of sample size

The sample size for this study is not derived from any power based calculation. The number of evaluable subjects for the study is based on the all infants who are willing to take part in the current study. Considering approximately 20-40% reduction in the number of evaluable subjects due to dropouts and protocol violations from the primary study, Table 16 gives the estimated sample size of evaluable subjects that can be expected and the precision achieved with this sample for various expected values of seroprotection/booster response rates in terms of exact 95% confidence interval (CI).

Table 16 Exact 95% CI of the different values of observed response rate (booster response rate or seroprotection rate) for a sample size of 204-272 subjects)

Number of evaluable subjects	Observed seroprotection/response rate expressed as a percentage	Exact 2-sided 95% CI for this observed rate for a sample size of 204-272 subjects	
		Lower Limit (LL)	Upper Limit (UL)
272	80	74.9	84.7
	86	81.3	89.9
	92	88.4	95.2
	93	89.3	95.7
	94	90.6	96.6
	95	92.0	97.4
	96	92.9	98.0
	97	94.3	98.7
	98	95.8	99.4
	99	97.4	99.9
	100	98.7	100.0
238	80	74.6	85.1
	86	81.1	90.3
	92	87.8	95.1
	93	89.3	96.1
	94	90.3	96.7
	95	91.4	97.4
	96	92.9	98.3
	97	94.0	98.8
	98	95.8	99.5
	99	97.0	99.9
	100	98.5	100.0
204	80	74.3	85.6
	86	80.8	90.7
	92	87.6	95.5
	93	88.8	96.2
	94	90.0	96.9
	95	91.2	97.6
	96	92.4	98.3
	97	93.7	98.9
	98	95.1	99.5
	99	96.5	99.9
	100	98.2	100

Reference study:
DTPa-HBV-IPV 095 (Germany): Group primed with *Infanrix hexa* according to 2, 4, 6 schedule and received a booster dose of *Infanrix hexa* between 11-23 months.
DTPa-HBV-IPV 083 (Spain): Group primed with *Infanrix hexa* according to 2, 4, 6 schedule and received a booster dose of *Infanrix hexa* between 18-20 months of age.
DTPa-HBV-IPV 081 (Germany): Group primed with *Infanrix hexa* according to 3, 4, 5 schedule and received a booster dose of *Infanrix hexa* between 12-23 months of age.

The reference values (booster phase) considered for the above calculations are presented in Table 17.

Table 17 Reference values (booster phase)

(Amended 12 December 2016)

Reference Study	Observed seroprotection rates		Booster response for Pertussis antigens			Observed Seroprotection rates				
	D	T	PT	FHA	PRN	PRP	HBs	Anti-IPV1	Anti-IPV2	Anti-IPV3
DTPa-HBV-IPV-095	100.0% [97.7, 100]	100.0% [97.7,100]	93.3% [88.1, 96.8]	86.0% [79.6, 91.0]	98.1% [94.4, 99.6]	99.4% [96.5,100]	100% [97.7,100]	100% [97.5,100]	100% [97.5,100]	100% [97.5,100]
DTPa-HBV-IPV 083 [Full term infants (≥37 weeks)]	100.0% [94.7, 100],	98.5% [92.1, 100]	97% [89.5,99.6]	98.5% [92, 100]	98.5% [92,100]	100% [94.7,100]	98.5% [92.1,100]	100% [94.6,100]	100% [94.6,100]	100% [94.3,100]
DTPa-HBV-IPV 083 [Pre-term infants (<37 weeks)]	100.0% [95.7, 100]	100.0% [95.7, 100]	100% [95.7,100]	97.6% [91.7, 99.7]	100% [95.7,100]	100% [95.7,100]	91.6% [83.4,96.5]	100% [95.5,100]	100% [95.5,100]	100% [95.1,100]
DTPa-HBV-IPV 081	100.0% [96.8, 100]	100.0% [96.8, 100]	98.2% [93.8,99.8]	98.2% [93.8,99.8]	99.1% [95.2,100]	100% [96.8,100]	99.1% [95.2,100]	100% [96.6,100]	100% [96.6,100]	100% [96.3,100]
217744/054	***100.0% [97.9,100.0]***	***100.0% [97.9,100.0]***	***100.0% [97.8,100.0]***	***100.0% [97.8,100.0]***	***100.0% [97.9,100.0]***	***100.0% [97.9,100.0]***	***98.9 (95.9,99.9)***	***100.0% [97.6,100.0]***	***100.0% [97.5,100.0]***	***100.0% [97.5,100.0]***

DTPa-HBV-IPV 095 (Germany): Group primed with *Infanrix hexa* according to 2,4,6 schedule and received a booster dose of *Infanrix hexa* between 11-23 months.
DTPa-HBV-IPV 083 (Spain): Group primed with *Infanrix hexa* according to 2,4,6 schedule and received a booster dose of *Infanrix hexa* between 18-20 months of age.
DTPa-HBV-IPV 081 (Germany): Group primed with Infanrix hexa according to 3,4,5 schedule and received a booster dose of Infanrix hexa between 12-23 months of age
217744/054: Group receiving DTPa-HBV-IPV/Hib according to 3,5,11 schedule in Italy and Germany

10.4. Cohorts for Analyses

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

10.4.1. Total enrolled cohort

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

10.4.2. Total vaccinated cohort

The TVC will include all vaccinated subjects for whom data are available. **(Amended 12 December 2016)**

- 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.

10.4.3. 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]. **(Amended 12 December 2016)**
- who have received the booster dose ***of study vaccines*** in the current study. **(Amended 12 December 2016)**
- 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.

10.4.4. 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]. **(Amended 12 December 2016)**
- Who comply with the procedures and intervals defined in the protocol (refer to Table 5).

- Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 6.7.2 during the study).
- Who did not receive a product leading to elimination from an ATP analysis as listed in Section 6.7.2,
- Who did not present with a medical condition leading to elimination from an ATP analysis as listed in Section 6.8,
- 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.

10.5. Derived and transformed data

The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.

- A seronegative subject is a subject whose antibody concentration/titre is below the assay cut-off.
- A seropositive subject is a subject whose antibody concentration/titre is greater than or equal to the assay cut-off defined in Table 7.
- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU/ml.
  - Anti-tetanus antibody concentrations ≥ 0.1 IU/ml.
  - Anti-HBs antibody concentrations ≥ 10 mIU/mL.
  - Anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8.
  - Anti-PRP antibody concentrations ≥ 0.15 µg/ml.
- Other cut-offs to be considered:
  - 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.
- For the pneumococcal antigens, the threshold used for statistical analysis will depend on the final selected assay.
- Booster response to the PT, FHA and PRN antigens, is defined as:

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

Note: Due to ongoing re-validation of pertussis assays and potential change in the assay unit, the definition of booster response may be subject to change.

- The geometric mean titres (GMTs)/geometric mean concentrations (GMCs) calculations will be performed by taking the anti-log of the mean of the $\log_{10}$ titre/concentration transformations. Antibody titres/concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation. Note that as per assay specification for anti-HBs antibodies, results between the assay cut-off of 6.2 mIU/ml and 7.65 mIU/ml (= Lower limit of Quantification) will be quantified as 6.2 mIU/ml.

Handling of missing data:

Immunogenicity

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.

Safety/reactogenicity

- 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.

10.6. Analysis of demographics

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***; **(Amended 12 December 2016)**
- 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.

10.7. Analysis of immunogenicity

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.

10.8. Analysis of safety

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. **(Amended 12 December 2016)**
- 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.

10.9. Interpretation of analyses

All analyses will be conducted in a descriptive manner.

10.10. 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.

10.10.1. 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, SAEs and neurodevelopmental status. A statistical report and a clinical report will be written at that time.

10.10.2. Statistical considerations for interim analyses

No interim analysis is planned for this study.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data

item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor freezes completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g., audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy (Amended 12 December 2016)

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in paediatric population conducted in at least one EU member state will be posted on publicly available EMA registers within 6 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within 6 months in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

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APPENDIX A CLINICAL LABORATORIES

Table 18 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Clinical Laboratory Sciences (CLS), Rixensart	Biospecimen Reception-B7/44 Rue de l'Institut, 89 -B-1330 Rixensart-Belgium
GSK Biologicals CLS, Wavre-Nord Noir Epine	Avenue Fleming, 20-B-1300 Wavre-Belgium

Table 19 Outsourced laboratories

(Amended 12 December 2016)

Laboratory	Address
NÉOMED-LABS Inc.	525, Cartier Ouest Laval, Quebec Canada H7V 3S8
Q² Solutions ***Limited*** (UK)	***The Alba Campus*** ***Rosebank*** ***Livingston*** ***West Lothian, EH54 7EG*** ***Scotland,*** UK
Q² Solutions Nichols Institute	33608 Ortega Highway San Juan Capistrano, CA 92675-2042 USA
CEVAC-University of Gent	De Pintelaan, 185 Gent Belgium

APPENDIX B AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	201334 [DTPA (BOOSTRIX)-049 BST: 048]
EudraCT number	2014-001120-30
Amendment number:	Amendment 1
Amendment date:	12 December 2016
Co-ordinating author:	PPD, Lead Scientific Writer

Rationale/background for changes:

Given the fact that only infants born from mothers vaccinated in the study (116945 [DTPA (BOOSTRIX)-047) and vaccinated in the previous study 201330 [DTPA (BOOSTRIX)-048 PRI] can be enrolled in the current study, the enrolment in these studies has an impact on this current study (e.g. cohorts to be investigated). Initially, the DTPA (BOOSTRIX)-047 and DTPA (BOOSTRIX)-048 PRI studies were opened only in countries using 3-dose primary vaccination series plus a booster vaccination at 12 to 18 months of age against diphtheria, tetanus and pertussis in infants. Nevertheless, the 2-dose primary vaccination schedule with a booster vaccination at 11 to 13 months of age in infants is also meaningful for different regions in the world (e.g. Europe). It was therefore decided to open the DTPA (BOOSTRIX)-047 and DTPA (BOOSTRIX)-048 PRI, and therefore the current booster study to countries using 2-dose primary vaccination series with a booster vaccination at 11 to 13 months of age with the aim to increase the scientific value of the study and generate clinical data in diverse infant vaccination schedules. This protocol is amended to include the possibility to administered the booster vaccine dose at 11 to 13 months of age, in addition to the 12 to 18 months of age initially planned.

The notion of end of study was clarified and the Section 11.5 describing the posting of information on public registry was revised accordingly.

An inclusion criterion was updated to specify that only infant having received the full vaccination series as per protocol requirement in the study DTPA (BOOSTRIX)-048 PRI can be enrolled in the current study (and not only infant born from mother vaccinated in the DTPA (BOOSTRIX)-047).

Following a request from the Czech Republic, the phone call at 18 months may be replaced by a clinic visit if deemed preferable by the study team.

The vaccination sites were updated to allow vaccination either in the thigh or deltoid, according to the national recommendation, to comply with the Australian recommendations. The names and functions of the contributing authors have been updated. In addition, minor updates including typos, abbreviations, clarifications of wording were done throughout the document.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Contributing authors: The following changes have been made:

- PPD ***, Clinical and Epidemiology Project Leader (CEPL)***
- PPD , Clinical Research and Development Lead (CRDL)
- PPD ***and*** PPD , Clinical Research and Development Lead (Project-Level CRDL)
- PPD , Project Statistician
- PPD ***and*** PPD , Study Delivery Lead
- PPD ***,*** PPD , Clinical Laboratory Sciences (CLS) Clinical Read-Out Team Leader
- PPD , ***CLS Study Manager***
- PPD ***and*** PPD , Global Clinical Regulatory Affairs Representative
- PPD ***,*** PPD ***,*** PPD and PPD , Clinical Safety Representatives
- PPD , Global Patents Representative
- PPD , Study Data Manager
- PPD ***,*** PPD ***, Oversight data Manager*** ~~Portfolio Data Manager~~
- PPD ***and*** PPD , Senior Manager, Biometrics
- PPD ***and*** PPD , Vaccines Supply Coordinator
- PPD , Director, Global Medical Affairs
- PPD , Study Delivery Manager
- PPD ***and*** PPD , Local Delivery Lead, Australia
- PPD ***and*** PPD , Local Delivery Lead, Canada
- PPD ***and*** PPD , Local Delivery Lead, Spain
- PPD ***and*** PPD , Local Delivery Lead, Czech Republic
- PPD , Director/Local Medical Lead, Czech Republic
- PPD ***, Local Delivery Lead, Finland***
- PPD ***and*** PPD ***, Local Delivery Leads, Italy***

Synopsis: Rationale for the study

The present study will be performed to study the immunogenicity and safety of the booster dose of *Infanrix hexa* in infants who were born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery ***and who completed their primary vaccination series as per protocol requirement in study DTPA (BOOSTRIX)-048 PRI.***

Synopsis: Rationale for the study design

This phase IV study is a follow-up of the study 201330 [DTPA (BOOSTRIX)-048 PRI]. The immunogenicity and safety of *Infanrix hexa* when given as a booster dose ***according to the routine national/ local immunization schedule or as specified in the SPM*** will be evaluated. Subjects will receive *Prevenar 13* ***according to the routine national/ local immunization schedule or as specified in the SPM*** as a co-administered vaccine in this study.

This study will have two groups:

- 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 ~~participated in the~~ ***received full*** primary vaccination course ***as per protocol requirement*** in the study 201330 [DTPA (BOOSTRIX)-048 PRI]. All infants 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 ~~participated in the~~ ***received full*** primary vaccination course ***as per protocol requirement*** in the study 201330 [DTPA (BOOSTRIX)-048 PRI]. All infants 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***.

The study will be open-label since the treatment allocation is similar between the two groups. Also, the data related to the study groups will be unblinded at the end of study 116945 [DTPA (BOOSTRIX)-047].

Currently, the effect of *Boostrix* administered to mothers during pregnancy or immediately post-delivery on the neurodevelopment of infants is unknown. Therefore, the neurodevelopment of the subjects will be studied at 9 months and 18 months of age in this study. To assess ~~for~~ the neurodevelopmental status, the ***investigator or designate*** ~~subject's parent(s)/legally acceptable representatives [LAR(s)]~~ will ~~be asked to~~ complete a standardised developmental screening tool, Ages and Stages Questionnaire-3 (ASQ-3) via a paper questionnaire ***with subjects' parent(s)/LAR(s) during the study visits or phone call*** ~~and submit it to the centralised research coordinating centre or the site where the study will be conducted~~ [ASQ-3, 2016].

Synopsis: Study design

- Experimental design: Phase IV, open-label, non-randomised, ~~uncontrolled~~ 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****Visit 3 or*~~18 months of age~~) Visit 3 (~~13~~ ***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 Synopsis 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 ~~participated in the~~ ***received full*** primary vaccination course 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 ~~participated in the~~ ***received full*** primary vaccination course 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***.

Synopsis Table 1: Study groups and epoch foreseen in the study

Study Groups	Number of subjects*	Age (Min – Max)**	Epochs
			Epoch 001
dTpa Group	340	***11*** ~~12~~ months- ~~18~~ ***19*** months	x
Control Group	340	***11*** ~~12~~ months-~~18~~ ***19*** months	x

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

Synopsis Table 2: Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		dTpa Group	Control Group
Infanrix hexa	***DTPa-***~~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*** ~~12~~-18 months of age ***according to the routine national/ local immunization schedule or as specified in the SPM***.

- Blinding: Open-label.

  Note: The study personnel operating SBIR and the site staff will remain blinded towards the treatment allocation ***of the mother*** in ~~this study until the completion and unblinding of~~ study 116945 [DTPA (BOOSTRIX)-047] ~~, study 201330 [DTPA (BOOSTRIX)-048 PRI] and this study~~.

- 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 adverse events (AEs), unsolicited AEs will be reviewed by this committee ***as per approved IDMC charter***.

List of abbreviations

CRDL:	***Clinical Research and Development Lead***
EL.U/mL:	***ELISA Unit per milliter***
EoS:	***End of Study***
EPAR:	***European public assessment report***
GCP:	***Good Clinical Practice***
HHE:	***Hypotonic-Hyporesponsiveness Episode***
Hib:	*Haemophilus influenzae* type b
HIV:	***Human Immunodeficiency Virus***
~~**HRV:**~~	~~Human Rotavirus Vaccine~~
IB:	***Investigator Brochure***
ICF:	***Informed Consent Form***
ICH:	***International Conference on Harmonization***
IEC:	***Independent Ethics Committee***
IgG/ IgM:	***Immunoglobulin G/ M***
IM:	***Intramuscular***
IMP:	***Investigational Medicinal Products***
IRB:	***Institutional Review Board***
JCVI:	***Joint Committee on Vaccination and Immunization***

LL:	***Lower Limit***
LSLV:	***Last Subject Last Visit***
PI:	***Product Information***
RCC:	***Reverse Cumulative Curve***
~~**RDE:**~~	~~Remote Data Entry~~
RSI:	***Reference Safety Safety Information***
SDV:	***Source Document Verification***
SIDS:	***Sudden Infant Death Syndrome***
SPC:	***Summary of Product characteristics***
SPM:	***Study Procedure Manual***
SRT:	***Safety Review Team***
(e)TDF:	***(electronic) Temperature Excursion decision Form***
UK:	***United Kingdom***
UL:	***Upper Limit***

Glossary of terms

End of Study: ***(Synonym of End of Trial)***	***For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV).*** ***For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV***

Trademarks

Trademarks not owned by the GlaxoSmithKline group of companies
Prevenar 13® (Wyeth Pharmaceuticals Inc.; Marketed by Pfizer Inc. or ***Wyeth LLC, owner/Pfizer Canada Inc., Licensee***)

Generic description
Pneumococcal ~~Pneumococcal~~ 13-valent conjugate vaccine (diphtheria CRM_{197} protein)

Section 1.1. Background

The incidence again was highest in infants younger than one year of age and all of nine deaths due to pertussis occurred in unvaccinated infants three months of age and younger [***Centers for Disease Control and Prevention (***CDC), 2015; CDC, 2013].

1.2.1 Rationale for the study

All infants born to pregnant women who participated in study 116945 [DTPA (BOOSTRIX)-047] will be followed-up to study the immunogenicity and safety of ***GlaxoSmithKline*** (GSK) Biologicals' combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b vaccine (DTPa-HBV-IPV/Hib)*, Infanrix hexa,* given as primary and booster vaccination. Study 201330 [DTPA (BOOSTRIX)-048 PRI] will be conducted to assess the immunogenicity and safety of *Infanrix hexa* co-administered with *Prevenar 13* as the primary vaccination course.

The present study will be performed to study the immunogenicity and safety of the booster dose of *Infanrix hexa* in infants who were born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery ***and who completed their primary vaccination series in study DTPA (BOOSTRIX)-048 PRI.***.

1.2.2. Rationale for the study design

This phase IV study is a follow-up of the study 201330 [DTPA (BOOSTRIX)-048 PRI] where infants in both the groups received *Infanrix hexa* co-administered with *Prevenar 13* as part of the primary vaccination ***series***. The immunogenicity and safety of *Infanrix hexa* when given as a booster dose ***according to the routine national/ local immunization schedule or as specified in the SPM*** will be evaluated. Subjects will receive *Prevenar 13* ***according to the routine national/ local immunization schedule or as specified in the SPM*** as a co-administered vaccine in this study.

This study will have two groups:

- 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 ~~participated in the~~ ***received full*** primary vaccination course ***as per protocol requirement*** in the study 201330 [DTPA (BOOSTRIX)-048 PRI]. All infants 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 ~~participated in the~~ ***received full*** primary vaccination course ***as per protocol requirement*** in the study 201330 [DTPA (BOOSTRIX)-048 PRI]. All infants 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***.

Currently, the effect of *Boostrix* administered to mothers during pregnancy or immediately post-delivery on the neurodevelopment of infants is unknown. Therefore, the neurodevelopment of the subjects will be studied at 9 months and 18 months of age in this study. To assess ~~for~~ the neurodevelopmental status, the ***investigator or designate*** ~~subject's parent(s)/legally acceptable representatives [LAR(s)]~~ will ~~be asked to~~ complete a standardised developmental screening tool, Ages and Stages Questionnaire-3 (ASQ-3) via a paper questionnaire ***with subjects' parent(s)/LAR(s) during the study visits or phone call*** ~~and submit it to the centralised research coordinating centre or the site where the study will be conducted~~ [ASQ-3, 2016].

1.3. Benefit: Risk assessment

Please refer to the current Investigator Brochure ***(IB)*** for the summary of potential risks and benefits of *Infanrix hexa.*

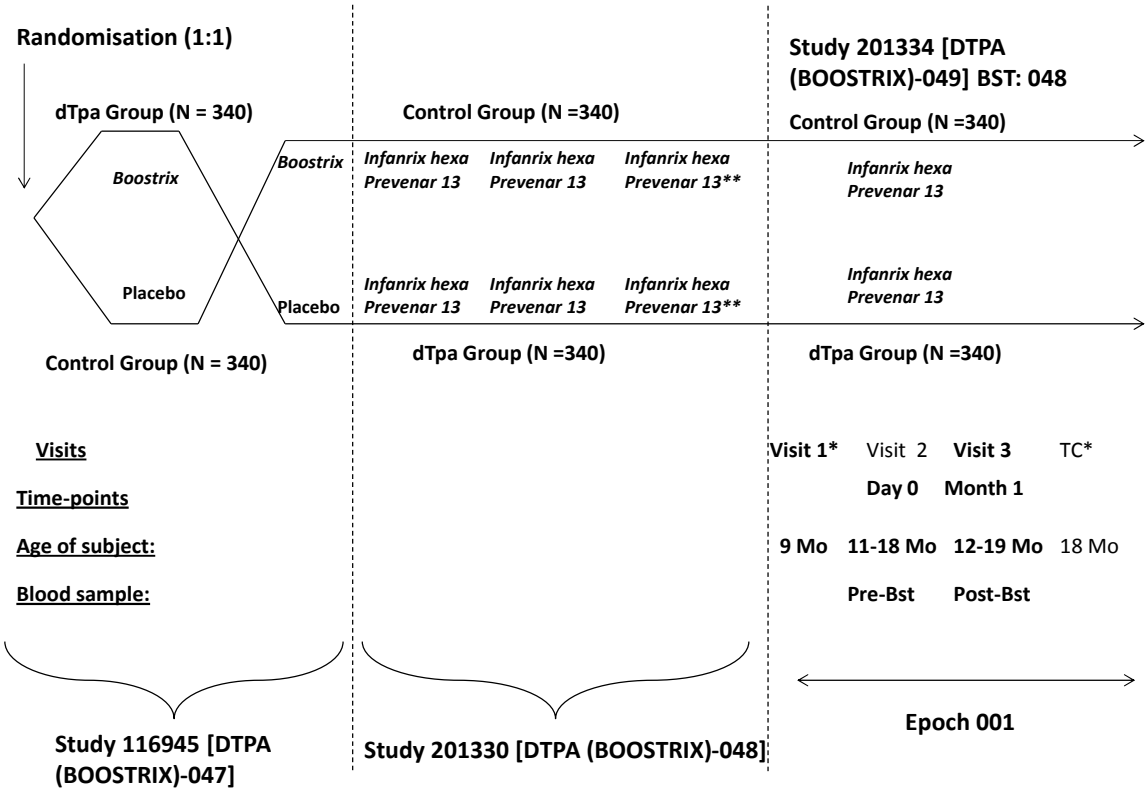
1.3.1. Risk assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational study vaccine *Infanrix hexa*		
Temperature of ≥ 40.0° C within 48 hours, not due to another identifiable cause	As outlined in the Infanrix hexa ***Reference Safety Information*** (RSI) from clinical trials and post-marketing safety data, this adverse event (AE)/serious adverse event (SAE) is recognized as well-characterized identified risks for Infanrix hexa.	Subjects' parents/LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.
Other *(Prevenar 13)*		
Temperature of ≥ 40.0° C within 48 hours, not due to another identifiable cause	As outlined in *Prevenar 13* European public assessment report (EPAR), increased fever rates were observed when *Prevenar 13* was co-administered with *Infanrix hexa*.	Subjects' parents/~~legally acceptable representative(s) [~~LAR(s) should report any untoward symptoms experienced by the infant after receiving the vaccine immediately to the investigator.

1.3.2. Benefit assessment

Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b (Hib) are common causes of diseases in children worldwide, with significant morbidity and mortality. A dramatic decline in the incidence of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Hib has been evidenced in countries in which infants are routinely immunised against these diseases. By receiving the *Infanrix hexa* vaccine, the subjects may be protected against the above mentioned diseases. In addition, the subjects will undergo a ~~history directed~~ physical examination at Visit 2 before booster vaccination. In case the study doctor discovers any medical condition, the subject will be referred to the local healthcare system. The vaccine and study related tests will be provided free of cost to the subjects.

3. Study design overview



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 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.

- Experimental design: Phase IV, open-label, non-randomised, ~~uncontrolled~~, 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 ~~(18 months of age)~~ or ***at*** Visit 3 ***(18 or 19 months of age)*** ~~(13-19 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 ~~participated in the~~ ***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 ~~participated in the~~ ***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 ~~12~~ months-~~18~~ ***19*** months	x
Control Group	340	***11*** ~~12~~ months-~~18~~ ***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	***DTP a***~~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***~~12~~-18 months of age ***according to the routine national/ local immunization schedule or as specified in the SPM***.
- Blinding: Open-label. Note: The study personnel operating ***GSK Biologicals' central Randomisation System on Internet (***SBIR) and the site staff will remain blinded towards the treatment allocation ***of the mother*** in ~~this study until the completion and unblinding of~~ study 116945 [DTPA (BOOSTRIX)-047]~~, study 201330 [DTPA (BOOSTRIX)-048 PRI] and this study~~.

- 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***.

4.1. Number of subjects/ centres

A maximum of 680 infants aged 9 months will be enrolled in this study. Blood samples will be taken from all subjects in order to evaluate the immunogenicity endpoints. The tracking of recruitment of subjects into the study will be performed using ~~GSK Biologicals' central randomisation system on Internet (~~SBIR~~)~~.

Overview of the recruitment plan:

- Enrolment will be offered to all eligible infants born to mothers from the 116945 [DTPA (BOOSTRIX)-047] study ***and having completed their primary vaccination series as per protocol requirement in study 201330 [DTPA (BOOSTRIX)-048 PRI]***.

4.2. Inclusion criteria

- 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]***.

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with the ***International Conference on Harmonization*** (ICH) Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

5.2.1. Subject identification

Subjects will retain the same subject number as their mothers in the 116945 [DTPA (BOOSTRIX)-047] study ***and their own subject number in study 201330 [DTPA (BOOSTRIX)-048 PRI]***. These subject numbers will also be used to identify blood samples collected in the study.

5.2.2.1. Treatment allocation to the subject

There will be no randomisation of subjects into groups in this study. The infants enrolled in this study will be allocated to the same groups as their mothers in the 116945 [DTPA (BOOSTRIX)-047] study ***and as themselves in study 201330 [DTPA (BOOSTRIX)-048 PRI]***. Subjects will retain the same subject number as their corresponding mothers from the 116945 [DTPA (BOOSTRIX)-047] study.

5.2.2.1.1. Study group and treatment number allocation

After obtaining the signed and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, ***investigator or designate will complete a***

standardised developmental screening tool, Ages and Stages Questionnaire-3 via a paper questionnaire (at Visit 1) with subjects' parent(s)/LAR(s) ~~will complete a standardised developmental screening tool, Ages and Stages Questionnaire-3 via a paper questionnaire (at Visit 1) at the study site~~. At Visit 2, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will provide the treatment number to be used for the ~~dose~~ ***vaccination***.

5.3. Method of blinding

Note: The study personnel operating SBIR and the site staff will remain blinded towards the treatment allocation ***of the mother in study 116945 [DTPA (BOOSTRIX)-047]*** ~~in this study~~ until the completion and unblinding of study 116945 [DTPA (BOOSTRIX)-047]~~,~~ ~~study 201330 [DTPA (BOOSTRIX)-048 PRI] and this study~~ to prevent the potential unblinding of the treatment allocation to the mother in 116945 [DTPA (BOOSTRIX)-047].

5.4.1. Independent Data Monitoring Committee

An IDMC will oversee the safety of infants born to mothers who were vaccinated with *Boostrix* during pregnancy or immediately post-delivery in the clinical study 116945 [DTPA (BOOSTRIX)-047], infants who received primary vaccination series of *Infanrix hexa* and *Prevenar13* ***as per protocol requirement*** in the study 201330 [DTPA (BOOSTRIX)-048 PRI] and booster vaccination in 201334 [DTPA (BOOSTRIX)-049 BST: 048] study.

To facilitate the review, the IDMC will be provided with all relevant safety data including data on each SAE, ~~/incidence of~~ grade 3 local and general solicited AEs, unsolicited AEs and neurodevelopmental status of infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery at specified times and access to data on request by an unblinded statistician. The frequency of the meeting will be ~~decided~~ ***and documented in the IDMC charter***

The operating rules of the IDMC ***are*** ~~will be~~ documented in a charter.

5.4.2. Responsabilities

The overall responsibility of the IDMC is to protect the ethical and safety interests of ~~patients~~ ***subjects*** recruited into this study while protecting as far as possible the scientific validity of the data.

The details of the IDMC's responsibilities and conduct of meetings will be provided in the IDMC ***c***~~C~~harter. The IDMC charter will also clearly state who will conduct the statistical analysis (ICH E9). Key responsibilities of the IDMC are the following:

- ***The IDMC will be informed of any amendment to the initial protocol***
- The IDMC will review the ***unblinded*** safety data from the study (i.e., each SAE~~/incidence of~~, grade 3 local and general solicited AEs , unsolicited AEs ***and neurodevelopmental status***), provide GSK Biologicals with indications on safety

profiles and make recommendations for consultation of regulatory authorities and on further study conduct.

5.4.3. Composition of the IDMC

IDMC members will not participate in the study, neither as principal or co-investigators nor as study ~~patient~~ ***subject*** care physicians. They can also not provide medical care to a ~~patient~~ ***subject*** enrolled in the study. The IDMC will include medically qualified experts in the field under study (paediatrician and a biostatistician). The person specifically selected to chair the IDMC will be required not only to have appropriate training for the study but also to have experience serving on one or more IDMCs. The IDMC also may convene an ad-hoc meeting should it deem necessary for review of specific cases/safety concerns.

5.4.4. GSK Biologicals' safety review team

A***t GSK Biologicals, a*** Safety Review Team ***(SRT) will include***~~, including~~ the Central Safety Physician ***and Safety Scientist***, the ***Clinical Research and development Lead (***CRDL) and Biostatistician of the project as well as Epidemiology and Regulatory representatives***.*** ***The SRT***~~, as core members and the IDMC~~ will be responsible for reviewing the ***blinded*** safety data related to the investigational product in this study and due to *Boostrix* vaccine ~~as~~ received by the mother in 116945 [DTPA (BOOSTRIX)-047] study***.*** ***The SRT review will be done*** on a regular basis to identify any potential safety issues or signals in order to evaluate and agree on action plans, if necessary.

The IDMC will provide recommendation to the sponsor ~~via the GSK Safety Review Team~~ ***which will be shared with the investigators***.

5.5. Outline of study procedures

Table 4 List of study procedures

Age	**9 months**	***11~~12~~*-18 months**	***12~~13~~*-19 months**	**18 months ****
Epoch		**Epoch 001**		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Phone contact ***
Time points	~~Day 0~~ ***Months -2 to -9***	~~Months 3 to 9~~ ***Day 0*** **	~~Months 4 to 10~~ ***Month 1*** **	~~9 Months~~ **Day 0 to Month7 ****
Sampling time points		**Pre-Bst**	**Post-Bst**	
Physical examination		***O*** ~~•~~		
Recording of solicited adverse events (Day 0-Day 3) ***post-vaccination*** by subjects' parent(s)/LAR(s) in the diary card		•		

* ***For Czech Republic, the phone call at 18 months may be replaced by a clinic visit if deemed preferable by the study team.***

** The neurodevelopmental status will be recorded when the subject is 9 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. If the subject is referred to a developmental specialist for formal assessment, then this information needs to be recorded in the eCRF. Also, the overall assessment of delay by the specialist should be recorded in the eCRF.

§ History of all medications given to the infants after the end of 201330 [DTPA (BOOSTRIX)-048 PRI] until enrolment in this study will be recorded in the eCRF ***at Visit 1 and updated at Visit 2 for all new information***

Table 5: Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval [2]
Birth→Visit 1	9 months old	9 months old* +30 days
Visit 1→Visit 2	***2*** ~~3~~ ***10*** ~~9~~ months **	***2*** ~~3~~ ***10*** months
Visit 2 → Visit 3	30 days	21-48 days
Phone contact	18 months old	18 months old* ± 30 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects will not be eligible for inclusion in the ATP cohort for analysis of immunogenicity if they make the study visit outside this interval.
* ***The allowed interval for Visit 1 and Phone contact is calculated depending on the official recommendation for age for completion of the ASQ-3 questionnaire (9 months and 0 days through 9 months and 30 days and 17 months and 0 days through 18 months of age and 30 days).*** In case subjects who were born prematurely by three or more weeks are enrolled, prematurity adjustment needs to be performed for the 9th and 18th month ASQ-3 questionnaire completion. Refer to Section 5.6.2.13 and SPM for more details.
** ***The intervals required in the table are the minimum and maximum intervals for the study and the allowed intervals for inclusion in the ATP cohort will correspond to approximately 30 days before or after the time window corresponding to the national/ local immunization schedule or as specified in the SPM***
If subjects return for the ~~visits~~ ***Visit 3*** prior to 30 days, the parent(s)/LAR(s) should take home the diary card and continue to record unsolicited safety information until 30 days post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects' parent(s)/LAR(s) who have not mailed/sent them in.

5.6.1.1. Informed consent

At the end of the primary vaccination series study, 201330 [DTPA (BOOSTRIX)-048 PRI], parent(s)/LAR(s) will be informed about this booster follow-up study [DTPA (BOOSTRIX)-049 BST: 048] in which their infants will receive a booster dose of the study vaccines. When the subject is approximately 9 months of age, the ***investigator or designee*** ~~subject's parent(s)/legally acceptable representatives [LAR(s)]~~ will ~~be asked to~~ complete a standardised developmental screening tool, Ages and Stages Questionnaire-3 (ASQ-3) via a paper questionnaire ***with subjects' parent(s)/LAR(s) during the*** ~~(at~~ Visit 1~~) at the study site~~.

5.6.2.2. Collect demographic data ~~and vital signs~~

Record demographic data such as ***the full date of birth*** ~~(age in months and race, length [cm], weight [kg] and head circumference [in (cm)])~~ in the subject's eCRF at Visit 2.

5.6.2.3. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record ***in the eCRF*** any pre-existing conditions or signs and/or symptoms present in a subject ~~prior to the study vaccination in the eCRF~~ at Visit 1 ***and update with all new information at Visit*** 2.

All events that occur after the end of primary study 201330 [DTPA (BOOSTRIX)-048 PRI] until enrolment in 201334 [DTPA (BOOSTRIX)-049 BST: 048] study ~~and are not reported to the investigator~~ will be recorded as part of the subject's medical history ~~and will be analysed in this study~~.

5.6.2.4. Medication and vaccination history

Obtain the subject's medication and vaccination history by interview and/or review of the subject's medical records and record ***in the eCRF*** any medication and vaccine administration ~~prior to the study vaccination in the eCRF~~ at Visits 1 and ***update with all new information at Visit*** 2.

5.6.2.5. Physical examination

Perform a physical examination (***including vital signs)*** prior to vaccination (Visit 2). ***The extend of the physical examination to be performed are as per investigator or delegate discretion to determine if the subject is healthy.***

If ***it is determined*** ~~determines that~~ that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled. Collected information needs to be recorded in the eCRF.

5.6.2.8. Record body length, weight and head circumference

Record body weight (kg), height (cm) and head circumference (cm) of the subject at Visit 2 in the eCRF.

5.6.2.11 Study vaccines administration

After completing all prerequisite procedures prior to vaccination, a booster dose of study vaccines will be administered intramuscularly (IM) ***either*** in the thigh ***or in the deltoid, according to the national recommendation /local practice*** .

5.6.2.13. Assessment of neurodevelopmental status

The ASQ-3 will be completed by the ***investigator or designee with*** the parent(s)/LAR(s) ***during the study visits or phone call*** when the subject is 9 and 18 months of age, via a paper questionnaire ~~and submitted to the centralised research coordinating centre or the site where the study will be conducted~~*. These time- points comply with the recommended developmental screening assessment guidelines from the American Academy of Pediatrics [Council on Children with Disabilities, 2006]. ***The investigator or designee may discuss the results with the parents if deemded necessary.***

The ASQ-3 has narrow age intervals ***(9 months and 0 days through 9 months and 30 days and 17 months and 0 days through 18 months of age and 30 days)***, so age must be calculated to the month and day from the date the ASQ-3 will be completed ~~(i.e., at 9 months and 18 months of age)~~.

*Note: It is encouraged that the parent(s)/LAR(s) of the subject complete the ASQ-3 during their visit to the study centre at Visit 2 or Visit 3. In case the subject completes Visit 3 before 18 months of age, the study staff will contact the parents/LAR(s) via phone to 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.***

5.6.2.14. Recording of AEs and SAEs

- Any unreturned diary cards will be sought from the subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure. The investigator/ ***designee*** will transcribe the collected information into the eCRF in English.

5.7. Biological sample handling and analysis

Please refer to the SPM ***and laboratory manual*** for details on biospecimen management (handling, storage and shipment).

5.7.1. Use of specified study materials

The use of other materials could result in the exclusion of the subject from the ***According-to-Protocol (***ATP) analysis (See Section 10.4 for the definition of cohorts to be analysed).

5.7.3. Laboratory assays

Table 7 Humoral immunity (antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off***	Laboratory †
SER	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	NA	IU/ml	***0***.1	GSK Biologicals*
SER	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	NA	IU/ml	***0***.1	GSK Biologicals*
SER	Haemophilus influenzae type b.Polyribosyl Ribitol Phosphate Ab	ELI	NA	µg/ml	***0***.15	GSK Biologicals*
SER	Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG Streptococcus pneumoniae.Polysaccharide 03 Ab.IgG Streptococcus pneumoniae.Polysaccharide 05 Ab.IgG Streptococcus pneumoniae.Polysaccharide 06A Ab.IgG Streptococcus pneumoniae.Polysaccharide 06B Ab.IgG Streptococcus pneumoniae.Polysaccharide 07F Ab.IgG Streptococcus pneumoniae.Polysaccharide 09V Ab.IgG Streptococcus pneumoniae.Polysaccharide 14 Ab.IgG Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG Streptococcus pneumoniae.Polysaccharide 19A Ab.IgG Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG	ELIF or multiplex	NA	µg/ml	***0***.05 or equivalent cut-off for the multiplex	GSK Biologicals*

System	Component	Method	Kit / Manufacturer	Unit	Cut-off***	Laboratory †
SER	Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG Streptococcus pneumoniae.Polysaccharide 03 Ab.IgG Streptococcus pneumoniae.Polysaccharide 04 Ab.IgG Streptococcus pneumoniae.Polysaccharide 05 Ab.IgG Streptococcus pneumoniae.Polysaccharide 06A Ab.IgG Streptococcus pneumoniae.Polysaccharide 06B Ab.IgG Streptococcus pneumoniae.Polysaccharide 07F Ab.IgG Streptococcus pneumoniae.Polysaccharide 09V Ab.IgG Streptococcus pneumoniae.Polysaccharide 14 Ab.IgG Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG Streptococcus pneumoniae.Polysaccharide 19A Ab.IgG Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG	ELI	NA	µg/ml	***0***.15	WHO reference laboratory**

*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Neomed Lab Inc, Canada.

** At the discretion of GSK Biologicals, pneumococcal testing may be done at a GSK Biologicals laboratory or the WHO reference laboratory

****** Assay cut-off and unit might be subject to change during the course of the study (e.g. in case of requalification, revalidation or standardization). In this case, this will be documented in the clinical report.***

† Refer to the APPENDIX A for the laboratory addresses.

~~*** The cut-offs for some of the assays might be subject to change due to assay re-development.~~

SER = Serum
ELI = Enzyme-linked immunosorbent assay (ELISA)
ELIF = 22F Inhibition ELISA
NEU = Neutralisation assay
CLIA = ChemiLuminescence ImmunoAssay
IU/mL = International Units/millilitre
mIU/mL = milliInternational Units/millilitre
EL.U/mL = ELISA Units/millilitre

µg/ml = Micrograms/millilitre
~~Note: The assay cut-off for D, T, pertussis and PRP may be subject to change.~~
~~The unit for the pertussis assays may be subject to change.~~

5.7.4.1. Immunological read-outs

Table 8: Immunological read-outs

Blood sampling time point		No. subjects	Component	Components priority rank
Type of contact and time point	Sampling time point			
Visit 2 (***Day 0*** ~~Month 3-9~~)	Pre-Bst	All	PT, FHA, PRN D, T HBs, PRP Poliovirus types 1, 2, 3 13 pneumococcal serotypes	1 2 3 4 5
Visit 3 (***Day 30*** ~~Month 4 - 10~~)	Post-Bst	All	 Poliovirus types 1, 2, 3 13 pneumococcal serotypes	1 2 3 4 5

Section 6.3. Dosage and administration of study vaccines

Table 10 Dosage and administration

Type of contact and time point	Volume to be administered	Study group	Treatment name	Route [1]	Site ~~[2]~~	Side [3]
Visit 2 (***Day 0*** ~~Month 3-9~~)	0.5 mL	dTpa Group and Control Group	*Infanrix hexa*	IM	~~T~~***Thigh or Deltoid*** [2]	R
Visit 2 (***Day 30*** ~~Month 3-9~~)	0.5 mL	dTpa Group and Control Group	*Prevenar 13*	IM	~~T~~***Thigh or Deltoid*** [2]	L

[1]Intramuscular (IM)
[2] ***The vaccines should be administered in the thigh or deltoid, according to the national recommendations***
~~Thigh (T)~~
[3]Right (R), Left (L)

6.6. Warnings and precautions

The information below presents, in addition to the contraindications in Section 6.5, warnings and precautions to administration of *Infanrix hexa.*

- If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:
  - Collapse or shock-like state (hypotonic-hyporesponsiveness episode ***[HHE]***) within 48 hours of vaccination.
- Increased reporting rates of convulsions (with or without fever) and ~~hypotonic hyporesponsive episode (~~HHE~~)~~ were observed with concomitant administration of *Infanrix hexa* and *Prevenar 13.*

Warnings and Precautions for the use of *Prevenar13:*

- Increased reporting rates of convulsions (with or without fever) and ~~hypotonic hyporesponsive episode (~~HHE~~)~~ were observed with concomitant administration of *Infanrix hexa* and *Prevenar 13.*

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period starting from the administration of the dose of study vaccines (Visit 2) and ending at ~~the last study visit (~~Visit 3 ***(Day 0 to Day 30)***~~).~~
- Any concomitant vaccination administered in the period starting from the administration of the dose of study vaccines (Visit 2) and ending at the ~~last~~ study visit ***3 (Day 0 to Day 30)*** ~~(Visit 3)~~.

8.2.1. Time period for detecting and recording adverse events and serious adverse events

The time period for collecting and recording SAEs will begin at the receipt of study vaccines and will end ~~30 days following administration of the dose of study vaccines~~ ***when the subject is discharged from the study.*** See Section 8.3 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time ***the subjects have been enrolled in the study*** ~~of the receipt of study vaccines~~.

Table 13 Reporting periods for collecting safety information

Event	V 1	V2	4 d post V2	31 d post-V2	V3	Phone contact * Study Conclusion
Age of subject	**9 months**	***11 ~~12~~-18 months***			***12 ~~13~~-19 months***	**18 months¶**
Timepoint	***Month -9 to -2***	***~~M 3-9~~ Day 0***	***Day 3***	***Day 30***	***~~M 4-10~~ Day 30***	***Day 0 to Month 7***
AEs/SAEs leading to withdrawal from the study						
SAEs						

~~* i.e., consent obtained for vaccination.~~ Pre-V: pre-vaccination; V: Visit; Post-V: post-visit; D: Day, M: Month;

**** For Czech Republic, the phone call at 18 months may be replaced by a clinic visit if deemed preferable by the study team.***

¶ Neurodevelopmental status will be recorded at 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.
If the subject is referred to a developmental specialist for formal assessment, then this information needs to be recorded in the eCRF. Also, the overall assessment of delay by the specialist should be recorded in the eCRF.

8.2.3.2.1. Assessment of intensity

The maximum intensity of fever ***(oral, axillary or typmpanic route)*** will be scored at GSK Biologicals as follows:

8.2.3.2.2. Assessment of causality

The investigator will also consult the IB and/or ***PI*** ~~Prescribing Information~~ for marketed products to determine his/her assessment.

10.3. Determination of sample size

Table 17 Reference values (booster phase)

Reference Study	Observed seroprotection rates		Booster response for Pertussis antigens			Observed Seroprotection rates				
	D	T	PT	FHA	PRN	PRP	HBs	Anti-IPV1	Anti-IPV2	Anti-IPV3
217744/054	*100.0% [97.9,100.0]*	*100.0% [97.9,100.0]*	*100.0% [97.8,100.0]*	*100.0% [97.8,100.0]*	*100.0% [97.9,100.0]*	*100.0% [97.9,100.0]*	*98.9 (95.9,99.9)*	*100.0% [97.6,100.0]*	*100.0% [97.5,100.0]*	*100.0% [97.5,100.0]*

217744/054: Group receiving DTPa-HBV-IPV/Hib according to 3,5,11 schedule in Italy and Germany

10.4.2. Total vaccinated cohort

The ~~Total Vaccinated cohort (~~TVC~~)~~ will include all vaccinated subjects for whom data are available.

10.4.3. 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*** ~~at least one~~ vaccine dose***s*** in the primary study DTPA (BOOSTRIX)-048 PRI.
- who have received the booster dose ***of study vaccines*** in the current study.

10.4.4. 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 received all ~~three~~ doses of vaccine in the primary study ***201330*** ~~201334~~ [DTPA (BOOSTRIX)-048 PRI].

10.6. analysis of demographics

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***;

10.7. analysis of immunogenicity

~~For serology results one month after the booster dose:~~

- 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.

~~The above summaries will be stratified based on country and primary vaccination schedule conducted as exploratory analysis.~~

10.8. Analysis of safety

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 ~~and overall~~, 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.

11.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in paediatric population conducted in at least one EU member state will be posted on publicly available EMA registers within 6 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within 6 months <u>in the concerned EU member state</u>, the summary of results shall be submitted as soon as it is available. In this case, <u>the protocol shall specify when the results are going to be submitted, together with a justification</u>.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

~~Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.~~

~~Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within six months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.~~

~~GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit. At the time of publication, this protocol will be fully disclosed.~~

Appendix A Clinical laboratories

Table 19 Outsources laboratories

Laboratory	Address
NÉOMED-LABS Inc.	525, Cartier Ouest Laval, Quebec Canada H7V 3S8
Q² Solutions ***Limited*** ~~Clinical Trials~~ (UK)	***The Alba Campus*** ***Rosebank*** ***Livingston*** ***West Lothian, EH54 7EG*** ***Scotland,*** ~~Unit B1, Parkway West Industrial Estate~~ ~~Cranford Lane Heston,~~ ~~Middlesex TW5 9QA~~ UK
Q² Solutions Nichols Institute	33608 Ortega Highway San Juan Capistrano, CA 92675-2042 USA
CEVAC-University of Gent	De Pintelaan, 185 Gent Belgium