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	201330 [DTPA (BOOSTRIX)-048 PRI]
EudraCT number	2014-001117-41
Date of protocol	Final Version 01: 13 February 2015
Date of protocol amendment	Amendment 1 Final: 06 September 2016
Title	Immunogenicity and safety study of GSK Biologicals' combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b vaccine (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 Infanrix hexa™ administered as primary vaccination in healthy infants born to mothers given Boostrix™ during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].
Co-ordinating author	PPD, Scientific Writer
Contributing authors ***(Amended 06 September 2016)***	• PPD, Clinical Research and Development Lead (CRDL) • PPD, ***Clinical and Epidemiology Project Leader (CEPL)*** • PPD, PPD ***and*** PPD, Project-Level CRDLs • PPD, Project Statistician • PPD, PPD ***and*** PPD, Study Delivery Leads

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Contributing authors ***(Amended 06 September 2016)***	• PPD, PPD ***and*** PPD ***CLS Study*** Managers • PPD ***and*** PPD ***,*** Global Clinical Regulatory Affairs Representatives • PPD, PPD and PPD, Clinical Safety Representatives • PPD, Global Patents Representative • PPD ***and*** PPD Study Data Managers • PPD ***, Project Data Manager*** • PPD ***and*** PPD Senior Managers, Biometrics • PPD ***and*** PPD, ***Clinical Trial Supplies Managers*** • PPD, Director, Global Medical Affairs • PPD ***and*** PPD ***,*** Local Delivery Leads • PPD ***and*** PPD ***, Local Delivery Leads*** • PPD ***and*** PPD, Local Delivery Leads • PPD ***, Local Delivery Lead*** • PPD ***, Local Delivery Lead*** • PPD ***and*** PPD ***, Local Delivery Leads***

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	201330 [DTPA (BOOSTRIX)-048 PRI]
EudraCT number	2014-001117-41
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Detailed Title	A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of Infanrix hexa™ administered as primary vaccination in healthy infants born to mothers given Boostrix™ during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].
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 Rationale

Amendment number:	Amendment 1

Rationale/background for changes:

Given the fact that only infants born from mothers vaccinated in the previous study (116945 [DTPA (BOOSTRIX)-047) can be enrolled in the current study, the enrolment in DTPA (BOOSTRIX)-047 study has an impact on this current study (e.g. cohorts to be investigated). Initially, the DTPA (BOOSTRIX)-047 study was opened only in countries using 3-dose primary vaccination series against diphtheria, tetanus and pertussis in infants. Nevertheless, the 2-dose primary vaccination schedule 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 therefore the current study to countries using 2-dose primary vaccination series in infants with the aim to increase the scientific value of the study and generate clinical data in diverse infant vaccination schedules.

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

The names and functions of the contributing authors have been updated. The name of GSK Biologicals' Global Vaccines Clinical Laboratories (GVCL) department has been updated to Clinical Laboratory Sciences (CLS) and the name of outsourced laboratory (Quest Diagnostic laboratory is now called Q² Solutions) has also 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 an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	201330 [DTPA (BOOSTRIX)-048 PRI]
EudraCT number	2014-001117-41
Date of protocol amendment	Amendment 1 Final: 06 September 2016
Detailed Title	A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of Infanrix hexa™ administered as primary vaccination in healthy infants born to mothers given Boostrix™ during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].
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 Infanrix hexa™ administered as primary vaccination in healthy infants born to mothers given Boostrix™ during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].
Indication	Primary 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 of Diphtheria-Tetanus-acellular Pertussis (DTPa) vaccination series. 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]. 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]. ***(Amended 06 September 2016)*** In 2013, the Advisory Committee on Immunisation Practices (ACIP) recommended that all women should be vaccinated with dTpa vaccine during each pregnancy, regardless of the previous immunisation schedule [CDC, 2013b]. Similar recommendations have been implemented in many countries including UK, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica, Argentina and some provinces in Australia and Spain [Joint Committee on Vaccination and Immunisation (JCVI), 2012; Pharmaceutical Management Agency (PHARMAC), 2012; TAG, 2013]. The National Advisory Committee on Immunisation 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]. ***(Amended 06 September 2016)***

In line with these recommendations, study 116945 [DTPA (BOOSTRIX)-047] will be conducted to evaluate the immunogenicity and safety of GlaxoSmithKline (GSK) Biologicals' dTpa vaccine, *Boostrix*, in pregnant women***, as well as the transfer of maternal antibodies against pertussis to the foetus (cord blood sample at delivery)***. Subjects will receive a dose of *Boostrix* during pregnancy or immediately post-delivery. ***(Amended 06 September 2016)***

All infants born to pregnant women who participate in study 116945 [DTPA (BOOSTRIX)-047] will be offered enrolment in the present study. This study will be conducted to evaluate 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 in the primary vaccination schedule. This will help us evaluate if the presence of transplacentally transferred maternal antibodies interfere with the immune response to primary vaccination with *Infanrix hexa* and a co-administered pneumococcal conjugate vaccine given as a part of this study in infants.

- Rationale for the study design

This phase IV study is a follow-up of the study 116945 [DTPA (BOOSTRIX)-047]. The immunogenicity and safety of *Infanrix hexa* when administered as a part of the primary vaccination schedule, ***according to the routine national immunisation schedule (3 doses given at 2, 4 and 6 months of age or at 2, 3 and 4 months of age or 2 doses given at 3 and 5 months of age or at 2 and 4 months of age)*** will be evaluated. ***As part of the study***, subjects will also receive *Prevenar 13* ***according to the routine national immunisation schedule***. The immunogenicity and safety of the booster dose of the same vaccines in infants in the second year of their life will be assessed in another follow-up study DTPA (BOOSTRIX)-049. ***(Amended 06 September 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. who received a single dose of *Boostrix* during pregnancy and a dose of placebo immediately post-delivery. All infants in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* ***according to the routine national immunisation schedule***. ***(Amended 06 September 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. who received a single dose of placebo during pregnancy and a dose of *Boostrix* immediately post-delivery. All infants in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* ***according to the routine national immunisation schedule***. ***(Amended 06 September 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].

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 vaccine response for the pertussis antigens, one month after the last dose of the primary vaccination in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.

Secondary

- To assess persistence of antibodies against diphtheria, tetanus and pertussis antigens, before the first dose of *Infanrix hexa* 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 last dose of the primary vaccination in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.

  *In some countries/regions with an ***Infanrix hexa 3-dose vaccination schedule***, *Prevenar 13* ***could be***

administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule). In such an instance, the evaluation will be ***performed one month after the last Infanrix hexa dose regardless of Prevenar 13 vaccination***. ***In the countries/regions with an Infanrix hexa 2-dose schedule, Prevenar 13 is co-administered at the same time as Infanrix hexa. (Amended 06 September 2016)***

- To assess the immunological response to *Infanrix hexa* in terms of seropositivity rates against pertussis antigens, one month after the last dose of the primary vaccination 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).

Study design

(Amended 06 September 2016)

- 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 3 months, per subject, for subjects vaccinated according to ***the 2 and 4, the 3 and 5 or*** the 2, 3 and 4 months schedule and approximately 5 months, per subject, for those vaccinated according to 2, 4 and 6 month schedule.
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 4 (Month ***3 or*** 5 ***depending on the vaccination schedule)***.
- ***End of Study (EoS): Last testing results released of samples collected at Visit 4.***
- Study groups: The study groups and epoch foreseen in the study are presented below.
  - dTpa Group: This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* ***according to the routine national immunisation schedule***.
  - Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047]. All subjects in this group will receive *Infanrix hexa* co-

administered with *Prevenar 13* ***according to the routine national immunisation schedule***.

Synopsis Table 1 Study groups and epoch foreseen in the study *(Amended 06 September 2016)*

Study Groups	Number of subjects	Age (Min - Max)*	Epoch
			Epoch 001
dTpa Group	340	6 -***14*** weeks	x
Control Group	340	6 -***14*** weeks	x

*Up to ***and including 14 weeks and 6 days of age***.

Synopsis Table 2 Study groups and treatments foreseen in the study *(Amended 06 September 2016)*

Treatment names	Vaccine name	Study Groups	
		dTpa Group	Control Group
Infanrix hexa	DTP***a***-HBV-IPV	x	x
	Hib	x	x
Prevenar 13	*Prevenar 13*	x	x

- Control: uncontrolled.
- Vaccination schedules: All subjects will receive ***either 3 doses of*** *Infanrix hexa* co-administered with *Prevenar 13** at 2, 4 and 6 months or 2, 3 and 4 months, ***either 2 doses of Infanrix hexa co-administered with Prevenar 13 at 3 and 5 months or at 2 and 4 months,*** depending on the immunisation schedule of the country.

  *In some countries/regions ***with an Infanrix hexa 3 doses routine national immunisation schedule***, *Prevenar 13* ***could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule)***. ***(Amended 06 September 2016)***
- Treatment allocation: non-randomised. All subjects will receive *Infanrix hexa* co-administered with *Prevenar 13.*
- Blinding: Open-label. Note: The study personnel operating GSK Biologicals' randomisation system on internet (SBIR) and the site staff will remain blinded towards the treatment allocation to subjects in study 116945 [DTPA (BOOSTRIX)-047].

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 timepoints ***(Amended 06***

September 2016):

- Pre-Pri: Before ***the first Infanrix hexa*** vaccine administration, a volume of approximately 2 mL of whole blood (to provide approximately 0.7 mL of serum) will be collected ***from all study participants***. ***(Amended 06 September 2016)***
- Post-Pri: One month after the last ***dose of Infanrix hexa*** primary vaccination, approximately 5 mL of whole blood (to provide approximately 1.7 mL of serum) will be collected ***from all study participants***. ***(Amended 06 September 2016)***

- Type of study: extension of other protocol(s) 116945 [DTPA (BOOSTRIX)-047].
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: An independent data monitoring committee (IDMC) (including paediatrician and statistician) will be put in place to oversee the safety of infants born to mothers who were vaccinated with *Boostrix* during pregnancy in the clinical study 116945 [DTPA (BOOSTRIX)-047] i.e. each SAE/incidence of grade 3 local and general solicited adverse events (A***E***s), unsolicited A***E***s will be reviewed by this committee ***as per IDMC approved charter***. ***(Amended 06 September 2016)***

Number of subjects *(Amended 06 September 2016)*

The target will be to enrol maximum of 680 eligible subjects aged 6-***14*** weeks (up to ***and including 14 weeks and 6 days of age***) (approximately 340 subjects in each group).

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 last dose of primary vaccination.
  - Vaccine response to PT, FHA and PRN antigens, one month after the last dose of primary vaccination.

Secondary

- Persistence of antibodies before the first dose of *Infanrix hexa*.
  - Anti-diphtheria and anti-tetanus seroprotection status,

anti-PT, anti-FHA, anti-PRN seropositivity status and antibody concentrations.

- Immunogenicity with respect to components of *Infanrix hexa* and *Prevenar 13*.
  - 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, one month after the last dose of primary vaccination.
- Immunogenicity with respect to components of *Infanrix hexa*.
  - Anti-PT, anti-FHA, anti-PRN antibody seropositivity status, one month after the last dose of primary vaccination.
- Solicited local and general symptoms.
  - Occurrence of solicited local/general symptoms during the 4-day (Day 0-Day 3) follow-up period after each vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited symptoms during the 31-day (Day 0-Day 30) follow-up period after each vaccination.
- Serious adverse events.
  - Occurrence of SAEs from first vaccination dose to study end.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF APPENDICES

PAGE

LIST OF ABBREVIATIONS

(Amended 06 September 2016)

ACIP:	Advisory Committee on Immunization Practices
AE:	Adverse Event
Anti-HBs:	Antibodies against hepatitis B surface antigen
ATP:	According-To-Protocol
CDC:	Centers for Disease Control and Prevention, USA
CEVAC:	***Centre for Vaccinology, Ghent University and Hospital***
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
DTP*a*-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:	***ELISA Units***
EOS	***End of study***
EPAR:	***European Public Assessment Report***
FHA:	Filamentous Haemagglutinin
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titre

GSK:	GlaxoSmithKline
HBs:	Hepatitis B surface antigen
HBV:	Hepatitis B Virus
HHE:	***Hypotonic Hyporesponsive Episode***
Hib:	*Haemophilus influenzae* type b
HRV:	Human Rotavirus Vaccine
IDMC:	Independent Data Monitoring Committee
IM:	***intramuscular***
IMP:	***Investigational Medicinal Product***
IPV:	Inactivated Poliovirus Vaccine
LAR:	Legally Acceptable Representative
MedDRA:	Medical Dictionary for Regulatory Activities
***(m)*IU:**	***(Milli)***-international units
PRN:	Pertactin
PRP:	Hib capsular polysaccharide Polyribosyl-Ribitol Phosphate
PT:	Pertussis Toxoid
RDE:	Remote Data Entry
RSI:	***Reference Safety Information***
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SCID:	***Severe Combined immunodeficiency Disease***
SDV:	***Source Document Verification***
SIDS:	***Sudden Infant Death Syndrome***
SPC:	Summary of Product Characteristics
SPM:	***Study Procedures Manual***

SRT	***Safety Review Team***
[e]TDF:	***(electronic) Temperature excursion Decision Form***
TT:	Tetanus Toxoid
TVC:	Total Vaccinated Cohort
USA/US:	United States of America
WHO:	World Health Organization

GLOSSARY OF TERMS (AMENDED 06 September 2016)

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)***	***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 timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints 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.
Intercurrent medical condition:	A condition that has the capability of altering a subject's immune response or are confirmed to have an immunodeficiency condition during the study.
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 authorized representative are used in some settings.)**	An individual or juridical or other body authorized 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 vaccines 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

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Prevenar 13® (Wyeth Pharmaceuticals Inc.; Marketed by Pfizer Inc.)	***Pneumococcal*** 13-valent conjugate vaccine (diphtheria CRM_{197} protein) ***(Amended 06 September 2016)***

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 2013, there were 24,231 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 [CDC, 2013a; CDC, 2013b].

In Canada, approximately 2500 cases were reported in 2012 [Public Health Agency of Canada, 2012]. The United Kingdom 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, 2012]. 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. 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, the findings that pre-existing high levels of pertussis antibody in infants suppress the ultimate immune response to whole-cell diphtheria, tetanus and pertussis (DTP) vaccines lessened the enthusiasm for this approach [Englund, 1995].

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 of DTPa vaccination series. 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].

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]. ***(Amended 06 September 2016)***

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, 2013b]. Similar recommendations have been implemented in 18 countries including UK, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica, Argentina and some provinces in Australia and 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]. ***(Amended 06 September 2016)***

In line with these recommendations, study 116945 [DTPA (BOOSTRIX)-047] will be conducted to evaluate the immunogenicity and safety of GlaxoSmithKline (GSK) Biologicals' dTpa vaccine, *Boostrix*, in pregnant women***, as well as the transfer of maternal antibodies against pertussis to the foetus (cord blood sample at delivery)***. Subjects will receive a dose of *Boostrix* during pregnancy or immediately post-delivery. ***(Amended 06 September 2016)***

All infants born to pregnant women who participate in study 116945 [DTPA (BOOSTRIX)-047] will be offered enrolment in the present study. This study will be conducted to evaluate 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 in the primary vaccination schedule. This will help us evaluate if the presence of transplacentally transferred maternal antibodies interfere with the immune response to primary vaccination with *Infanrix hexa* and a co-administered pneumococcal conjugate vaccine given as a part of this study in infants.

1.2.2. Rationale for the study design

This phase IV study is a follow-up of the study 116945 [DTPA (BOOSTRIX)-047]. The immunogenicity and safety of *Infanrix hexa* when administered as a part of the primary vaccination schedule, ***according to the routine national immunisation schedule (3 doses given at 2, 4 and 6 months of age or at 2, 3 and 4 months of age or 2 doses given at 3 and 5 months of age or at 2 and 4 months of age)*** will be evaluated. ***As part of the study*** subjects will also receive *Prevenar 13* ***according to the routine national immunisation schedule***. The immunogenicity and safety of the booster dose of the same vaccines in infants in the second year of their life will be assessed in another follow-up study DTPA (BOOSTRIX)-049. ***(Amended 06 September 2016)***

This study will have two groups ***(Amended 06 September 2016)***:

- dTpa Group: This group will consist of infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] i.e. who received a single dose of *Boostrix* during pregnancy and a dose of placebo immediately post-delivery. All infants in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* ***according to the routine national immunisation schedule***.
- Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047], i.e. who received a single dose of placebo during pregnancy and a dose of *Boostrix* immediately post-delivery. All infants in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* ***according to the routine national immunisation schedule***.

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].

1.3. Benefit : Risk Assessment

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

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 06 September 2016)***	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.
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.
Apnoea in infants born prematurely	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*.	Medically stable* prematurely born infants, born after a gestation period of 27-36 weeks may be enrolled in the study at the discretion of the investigator. The need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very preterm infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.
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.		

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
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 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 *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 06 September 2016)***
Apnoea in infants born prematurely	As outlined in *Prevenar 13* EPAR this AE/SAE is recognized as well-characterized identified risks for *Prevenar 13*.	Medically stable* prematurely born infants, born after a gestation period of 27-36 weeks may be enrolled in the study at the discretion of the investigator.
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.

*Medically stable refers to the condition of premature infants who do not require significant medical support or ongoing management for debilitating disease and who have demonstrated a clinical course of sustained recovery by the time they receive the first dose of study vaccine.

1.3.2. Benefit Assessment

Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b 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 *Haemophilus influenzae* type b 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 the first study visit. In case the study doctor discovers any medical condition, the subject will be referred to the local healthcare system. The vaccine and study tests will be provided free of cost to the subjects.

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 vaccine response to the pertussis antigens, one month after the last dose of the primary vaccination 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

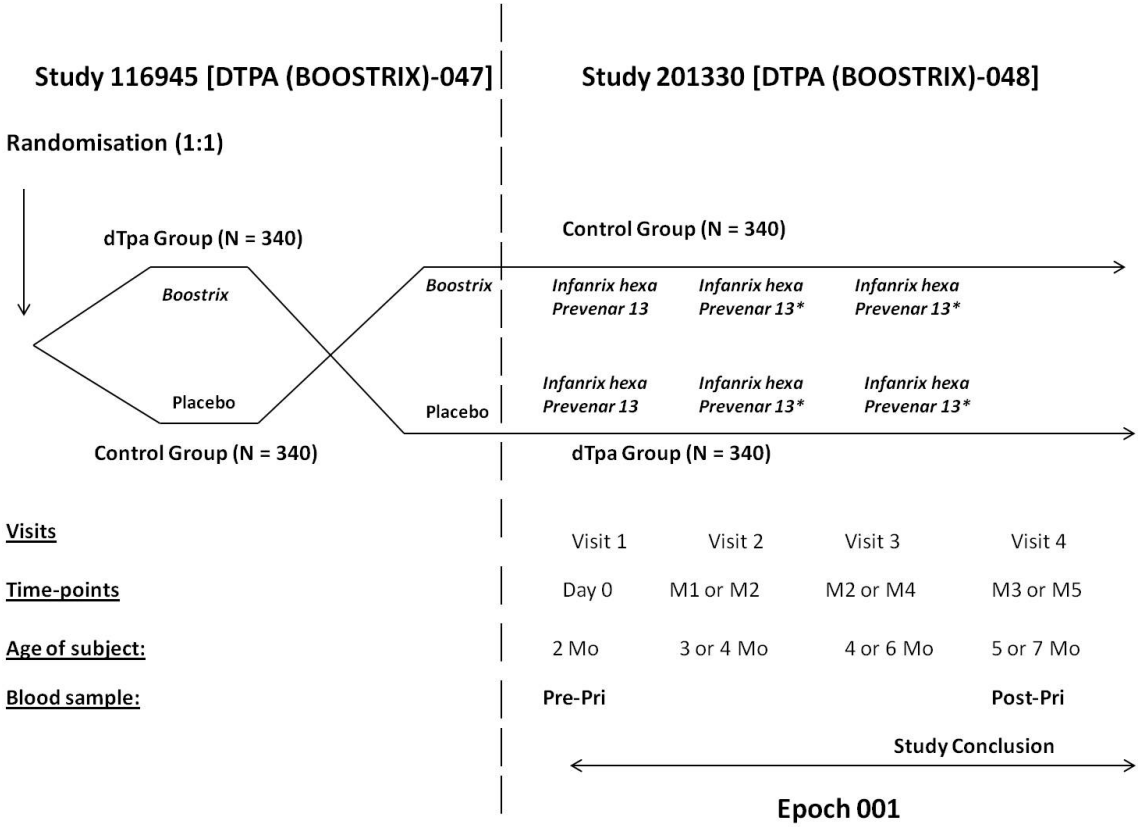
- To assess persistence of antibodies against diphtheria, tetanus and pertussis antigens, before the first dose of *Infanrix hexa* in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.
- To assess the immunological response to *Infanrix hexa* and *Prevenar 13* in terms of antibody concentrations or titres against all antigens, one month* after the last dose of the primary vaccination 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 last dose of the primary vaccination 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).

  *In some countries/regions with an ***Infanrix hexa 3-dose vaccination schedule***, *Prevenar 13* ***could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule)***. In such an instance, the evaluation will be ***performed one month after the last Infanrix hexa dose regardless of Prevenar 13 vaccination***. ***In the countries/regions with an Infanrix hexa 2-dose schedule, Prevenar 13 is co-administered at the same time as Infanrix hexa. (Amended 06 September 2016)***

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

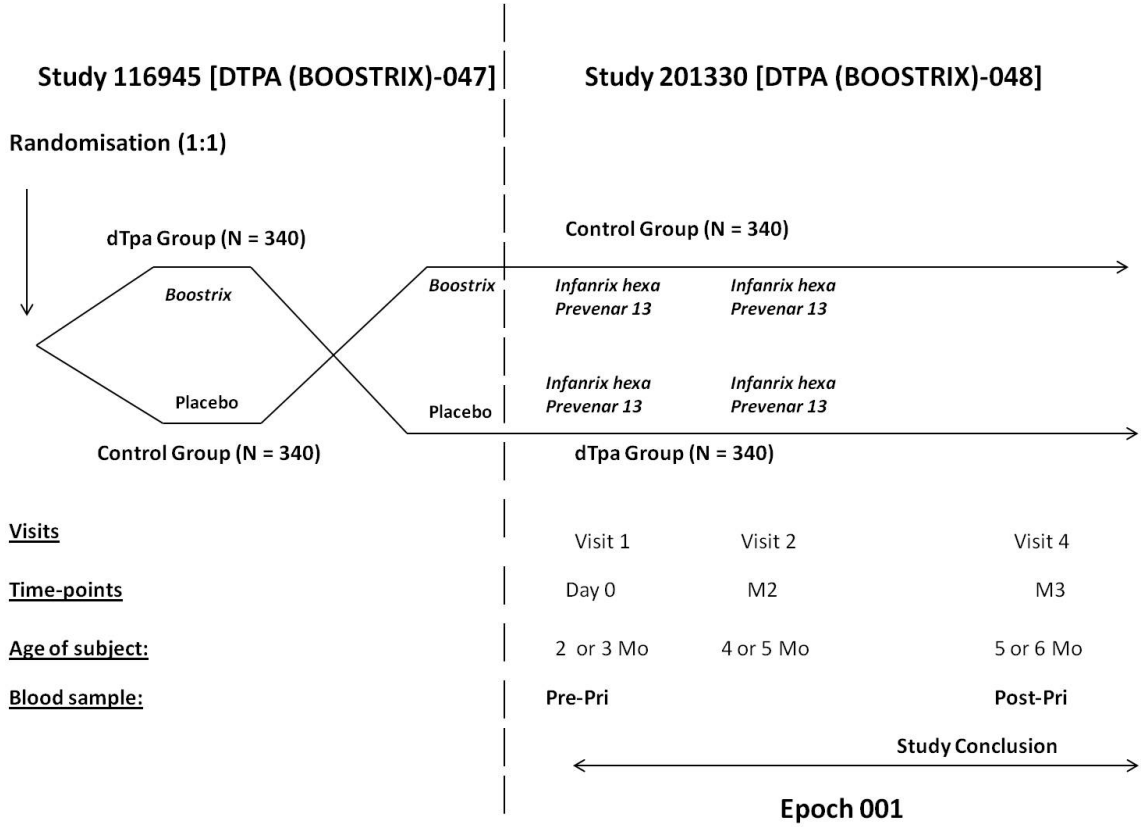
3. STUDY DESIGN OVERVIEW

Figure 1 Study design diagram for infants receiving a 3-dose schedule of Infanrix hexa (Amended 06 September 2016)



N: Maximum number of subjects planned to be enrolled
M = Month, Mo = age in months
Timepoints have been numbered based on the different vaccination schedules. D0, M1, M2 and M3 timepoints reflect for subjects who will be vaccinated according to the 2, 3 and 4 month schedule while D0, M2, M4 and M5 timepoints reflect for subjects who will be vaccinated according to the 2, 4 and 6 month schedule.
* In some countries/regions ***with an Infanrix hexa 3-dose schedule***, *Prevenar 13* is given as a 2-dose schedule at2 and 4 months of age as a part of the routine immunisation programme
Pre-Pri = Blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = Blood sample to be collected one month after the last dose of the primary vaccination course

Figure 2 Study design diagram for infants receiving a 2-dose schedule of Infanrix hexa (Amended 06 September 2016)



N: Maximum number of subjects planned to be enrolled
M = Month, Mo = age in months
Pre-Pri = Blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = Blood sample to be collected one month after the last dose of the primary vaccination course
Subjects will be vaccinated either at 2 and 4 months of age or 3 and 5 months of age, according to the routine national immunisation schedule

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 3 months, per subject, for subjects vaccinated according to ***the 2 and 4, the 3 and 5 or*** the 2, 3 and 4 months schedule and approximately 5 months, per subject, for those vaccinated according to 2, 4 and 6 month schedule. ***(Amended 06 September 2016)***
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 4 (Month ***3 or*** 5***, depending on the vaccination schedule). (Amended 06 September 2016)***

- ***End of Study (EoS): Last testing results released of samples collected at Visit 4.***

  Refer to the glossary of terms for the definition of EoS. (Amended 06 September 2016)

- Study groups: The study groups and epoch foreseen in the study are presented in Table 1.

Table 1 Study groups and epoch foreseen in the study *(Amended 06 September 2016)*

Study Groups	Number of subjects	Age (Min - Max)*	Epoch
			Epoch 001
dTpa Group	340	6-***14*** weeks	x
Control Group	340	6-***14*** weeks	x

*Up to ***and including 14 weeks and 6 days of age***.

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

Table 2 Study groups and treatments foreseen in the study *(Amended 06 September 2016)*

Treatment names	Vaccine name	Study Groups	
		dTpa Group	Control Group
Infanrix hexa	DTP***a***-HBV-IPV	x	x
	Hib	x	x
Prevenar 13	*Prevenar 13*	x	x

- Control: uncontrolled

- Vaccination schedules: All subjects will receive ***either 3 doses of*** *Infanrix hexa* co-administered with *Prevenar 13** at 2, 4 and 6 months or 2, 3 and 4 months, ***either 2 doses of Infanrix hexa co-administered with Prevenar 13 at 3 and 5 months or 2 and 4 months,*** depending on the immunisation schedule of the country.

  *In some countries/regions ***with an Infanrix hexa 3 doses routine national immunisation schedule***, *Prevenar 13* ***could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule)***. ***(Amended 06 September 2016)***

- Treatment allocation: non-randomised. All subjects will receive *Infanrix hexa* co-administered with *Prevenar 13.*

- Blinding: Open-label. Note: The study personnel operating GSK Biologicals' randomisation system on internet (SBIR) and the site staff will remain blinded towards the treatment allocation to subjects in study 116945 [DTPA (BOOSTRIX)-047]. ***(Amended 06 September 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 timepoints ***(Amended 06 September 2016)***:
  - Pre-Pri: Before ***the first Infanrix hexa*** vaccine administration, a volume of approximately 2 mL of whole blood (to provide approximately 0.7 mL of serum) will be collected ***from all study participants***.
  - Post-Pri: One month after the last ***dose of Infanrix hexa*** primary vaccination, approximately 5 mL of whole blood (to provide approximately 1.7 mL of serum) will be collected ***from all study participants***.
- Type of study: extension of other protocol(s) 116945 [DTPA (BOOSTRIX)-047].
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: An independent data monitoring committee (IDMC) (including paediatrician and statistician) will be put in place to oversee the safety of infants born to mothers who were vaccinated with *Boostrix* during pregnancy in the clinical study 116945 [DTPA (BOOSTRIX)-047] i.e. each SAE/incidence of grade 3 local and general solicited AEs, unsolicited AEs will be reviewed by this committee ***as per IDMC approved charter***. ***(Amended 06 September 2016)***

4. STUDY COHORT

4.1. Number of subjects/centres

A maximum of 680 infants aged 6-***14*** weeks (up to ***and including 14 weeks and 6 days of age***) 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. ***(Amended 06 September 2016)***

Overview of the recruitment plan:

- Enrolment will be terminated when all the eligible infants born to ***pregnant women*** from the 116945 [DTPA (BOOSTRIX)-047] study are enrolled. ***(Amended 06 September 2016)***
- The study will be monitored by a local Study Monitor.
- The treatment allocation and 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 jeopardize 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)/Legally Acceptable Representative(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 between, 6 and ***14*** weeks of age (including 6 weeks and up to ***and including 14 weeks and 6 days of age***) at the time of the first vaccination. ***(Amended 06 September 2016)***
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born to a mother enrolled in study 116945 [DTPA (BOOSTRIX)-047].
- Medically stable* prematurely born infants, born after a gestation period of 27-36 weeks may be enrolled in the study at the discretion of the investigator.

  *Medically stable refers to the condition of premature infants who do not require significant medical support or ongoing management for debilitating disease and who have demonstrated a clinical course of sustained recovery by the time they receive the first dose of study vaccine.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize 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.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting at birth prior to the first 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).
- Administration of any chronic drug therapy to be continued during the study period.
- A vaccine not foreseen by the study protocol administered during the period starting from 30 days before each dose of vaccine and ending 30 days after*, with the exception of 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 package insert (PI) and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination against Hib, diphtheria, tetanus, pertussis, pneumococcus, and/or poliovirus since birth.
- History of Hib, diphtheria, tetanus, pertussis, pneumococcal, poliovirus and hepatitis B diseases.
- Any confirmed or suspected immunosuppressive or immunodeficient condition including severe combined immunodeficiency disease (SCID), based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects
- Serious chronic illness.
- History of any neurological disorders or seizures.
- Acute disease and/or fever at the time of enrolment.
  - 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.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products during the period starting at birth before the first dose of study vaccines or planned administration during the study period.
- Hypersensitivity to latex.

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 ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

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.
- 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. These subject numbers will also be used to identify blood samples collected in the study.

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. Subjects will retain the same subject number as their corresponding mothers from the 116945 [DTPA (BOOSTRIX)-047] study.

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 6-***14*** weeks (up to ***and including 14 weeks and 6 days of age***) (approximately 340 subjects in each group). ***(Amended 06 September 2016)***

The central randomisation system on internet (SBIR) will be used at the investigator site to track enrolment to confirm or to cancel the vaccination and to give the treatment number associated with the vaccination.

After obtaining the signed and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, 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 first dose.

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.

5.2.2.1.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number and the system will provide a treatment number to be allocated.

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

5.3. Method of blinding

This study will be conducted in an open-label manner since the treatment 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 to subjects in study 116945 [DTPA (BOOSTRIX)-047]. ***(Amended 06 September 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 in the clinical study 116945 [DTPA (BOOSTRIX)-047].

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 ***and*** unsolicited AEs at specified times and access to data on request by an unblinded statistician. ***(Amended 06 September 2016)***

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

5.4.2. Responsibilities

(Amended 06 September 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 ***charter***. 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 ***and*** unsolicited AEs), provide GSK Biologicals with indications on safety profiles and make recommendations for consultation of regulatory authorities and on further study conduct.

- The IDMC will review the final analysis provided by the sponsor.

5.4.3. Composition of the IDMC (Amended 06 September 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 06 September 2016)

A***t GSK Biologicals, a*** Safety Review Team ***(SRT) will*** includ***e*** the Central Safety Physician, the ***Clinical Research and Development Lead (***CRDL) and Biostatistician of the project as well as Epidemiology and Regulatory representative. ***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 via the GSK ***SRT***.

5.5. Outline of study procedures

(Amended 06 September 2016)

The list of study procedures ***for infants receiving a 3-dose and a 2-dose schedule of Infanrix hexa*** is detailed below in Table 4 ***and Table 5, respectively***.

Table 4 List of study procedures *for infants receiving a 3-dose schedule of Infanrix hexa (Amended 06 September 2016)*

Age	2 months	3 or 4 months	4 or 6 months	5 or 7 months
Epoch	Epoch 001			
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4
Timepoints	Day 0	Month 1 or 2#	Month 2 or 4#	Month 3 or 5#
Sampling timepoints	Pre-Pri			Post-Pri
Informed consent	●			
Check inclusion/exclusion criteria	●			
Collect demographic data	●			
Medical history, including medication/vaccine history*	●			
History directed physical examination	●			
Check contraindications and warnings and precautions	○	○	○	
Record pre-vaccination body temperature	●	●	●	
Record body weight, height and head circumference	●			●
Study group and treatment number allocation	●			
Treatment number allocation for subsequent doses		○	○	
Recording of administered treatment number	●	●	●	
Blood sampling for antibody determination	●			●
Vaccine administration**	●	●	●	
Record any concomitant medication/vaccination	●	●	●	●
Record any intercurrent medical conditions		●	●	●
Distribution of diary cards	○	○	○	
Recording of solicited adverse events (Day 0- Day 3) by subjects' parent(s)/LAR(s)	●	●	●	
Recording of non-serious adverse events (Day 0-Day 30) by subjects' parent(s)/LAR(s)	●	●	●	●
Return of diary cards		○	○	○
Diary card transcription by investigator or site staff		●	●	●
Recording of SAEs	●●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●
Withdrawals due to AEs/SAEs	●	●	●	●
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.
Pre-Pri: Blood sample to be collected before the first dose of the primary vaccination course (~2 mL).
Post-Pri: Blood sample to be collected one month after the last dose of the primary vaccination course (~ 5 mL).
Depending on the immunisation schedule of the country.
* History of all medications given to the infants will be recorded in the eCRF.
** In some countries/regions ***with an Infanrix hexa 3-dose schedule***, *Prevenar 13* is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.

Timepoints have been numbered based on the different vaccination schedules. D0, M1, M2 and M3 timepoints reflect for subjects who will be vaccinated according to the 2, 3 and 4 month schedule while D0, M2, M4 and M5 timepoints reflect for subjects who will be vaccinated according to the 2, 4 and 6 month schedule.

Table 5 List of study procedures for infants receiving a 2-dose schedule of Infanrix hexa (Amended 06 September 2016)

Age	*2 or 3 months#*	*4 or 5 months#*		*5 or 6 months#*
Epoch	*Epoch 001*			
Type of contact	*Visit 1*	*Visit 2*	*Visit 3***	*Visit 4*
Timepoints	*Day 0*	*Month 2*		*Month 3*
Sampling timepoints	*Pre-Pri*			*Post-Pri*
Informed consent	●			
Check inclusion/exclusion criteria	●			
Collect demographic data	●			
*Medical history, including medication/vaccine history**	●			
History directed physical examination	●			
Check contraindications and warnings and precautions	O	O		
Record pre-vaccination body temperature	●	●		
Record body weight, height and head circumference	●			●
Study group and treatment number allocation	●			
Treatment number allocation for subsequent doses		O		
Recording of administered treatment number	●	●		
Blood sampling for antibody determination	●			●
Vaccine administration	●	●		
Record any concomitant medication/vaccination	●	●		●
Record any intercurrent medical conditions		●		●
Distribution of diary cards	O	O		
Recording of solicited adverse events (Day 0- Day 3) by subjects' parent(s)/LAR(s)	●	●		
Recording of non-serious adverse events (Day 0-Day 30) by subjects' parent(s)/LAR(s)	●	●		●
Return of diary cards		O		O
Diary card transcription by investigator or site staff		●		●
Recording of SAEs	●	●		●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●		●
Withdrawals due to AEs/SAEs	●	●		●
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.
Pre-Pri: Blood sample to be collected before the first dose of the primary vaccination course (~ 2 mL).
Post-Pri: Blood sample to be collected one month after the last dose of the primary vaccination course (~ 5 mL).
 # Depending on the immunisation schedule of the country.
** History of all medications given to the infants will be recorded in the eCRF.*
*** Subject receiving 2 doses of Infanrix hexa will not attend the Visit 3*

The intervals between study visits for subjects ***receiving 3 doses of Infanrix hexa*** at 2, 4 and 6 months and 2, 3 and 4 months are presented in Table 6 and Table 7, respectively. ***The intervals between study visits for subjects receiving 2 doses of Infanrix hexa at 2***

and 4 months and at 3 and 5 months are presented in Table 8 and Table 9, respectively. (Amended 06 September 2016)

Table 6 Intervals between study visits for subjects vaccinated *with Infanrix hexa* at 2, 4 and 6 months of age *(Amended 06 September 2016)*

Interval	Optimal length of interval [1]	Allowed interval[2†]
Birth →Visit 1	60 days	42-***104*** days
Visit 1→Visit 2	60 days	52 - 78 days
Visit 2→Visit 3	60 days	52 - 78 days
Visit 3→Visit 4	30 days *	21 -48 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.
† Date of previous visit/contact is the reference date
*If subjects return for the visits 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.

Table 7 Intervals between study visits for subjects vaccinated *with Infanrix hexa* at 2, 3 and 4 months of age *(Amended 06 September 2016)*

Interval	Optimal length of interval [1]	Allowed interval[2†]
Birth→Visit 1	60 days	42-***104*** days
Visit 1→Visit 2	30 days	21 -48 days
Visit 2→Visit 3	30 days	21 -48 days
Visit 3→Visit 4	30 days *	21 -48 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.
† Date of previous visit/contact is the reference date
*If subjects return for the visits 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.

Table 8 Intervals between study visits for subjects vaccinated with Infanrix hexa at 2 and 4 months of age (Amended 06 September 2016)

Interval	*Optimal length of interval [1]*	*Allowed interval[2†]*
Birth →Visit 1	***60 days***	***42-104 days***
Visit 1→Visit 2	***60 days***	***52-78 days***
Visit 2→Visit 4*	***30 days****	***21- 48 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.
† Date of previous visit/contact is the reference date
****If subjects return for the visits 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.***
***** Subject receiving 2 doses of Infanrix hexa will not attend the Visit 3***

Table 9 Intervals between study visits for subjects vaccinated with Infanrix hexa at 3 and 5 months of age (Amended 06 September 2016)

Interval	*Optimal length of interval [1]*	*Allowed interval[2†]*
Birth →Visit 1	*90 days*	*42-104 days*
Visit 1→Visit 2	*60 days*	*52-78 days*
*Visit 2→Visit 4***	*30 days**	*21-48 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.
† Date of previous visit/contact is the reference date
**If subjects return for the visits 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.*
*** Subject receiving 2 doses of Infanrix hexa will not attend the Visit 3*

5.6. Detailed description of study procedures

5.6.1. 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.

Note: At ***Visit 4***, parent(s)/LAR(s) will be informed about the booster follow-up study DTPA (BOOSTRIX)-049 BST: 048 in which their infants will receive a booster dose of the study vaccines ***according to the national immunisation programme***. ***(Amended 06 September 2016)***

5.6.2. Check inclusion and exclusion criteria

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

5.6.3. Collect demographic data

Record demographic data such as (age in weeks and race) in the subject's eCRF.

5.6.4. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF.

5.6.5. 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 any medication and vaccine administration prior to the study vaccination in the eCRF.

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5.6.6. History directed physical examination

Perform a history directed physical examination. If the investigator determines 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.

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.

5.6.7. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.8. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be rectal/axillary. 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 6 and Table 7 as applicable).

5.6.9. *Record body weight, height and* head circumference

(Amended 06 September 2016)

Record body weight (kg), height (cm) and head circumference (cm) of the infant at Visit 1 and Visit 4 in the eCRF.

5.6.10. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.11. Sampling

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

5.6.11.1. Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- Pre-Pri: Before ***the first Infanrix hexa*** vaccine administration, a volume of approximately 2 mL of whole blood (to provide approximately 0.7 mL of serum) will be collected. ***(Amended 06 September 2016)***
- Post-Pri: One month after the last ***dose of Infanrix hexa*** primary vaccination at Visit 4, approximately 5 mL of whole blood (to provide approximately 1.7 mL of serum) will be collected. ***(Amended 06 September 2016)***
- After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM ***and laboratory manual*** for more details on sample storage conditions. ***(Amended 06 September 2016)***

5.6.12. Study *vaccine* administration

(Amended 06 September 2016)

- After completing all prerequisite procedures prior to vaccination, study vaccines will be administered intramuscularly (IM) in ***the thigh*** as described in Section 6.3. If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccination, the visit will be rescheduled within the allowed interval for this visit (see Table 6 ***to Table 9,*** as applicable).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine with appropriate medical treatment readily available in case of anaphylaxis.

5.6.13. 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.

5.6.14. 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.
- At each vaccination visit, diary cards will be provided to the subject's parent(s)/LAR(s) with instructions by the study staff. The subject's parent(s)/LAR(s) will record body (rectal/axillary) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next 3 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 ***the next visit***. ***(Amended 06 September 2016)***
- 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 or site staff will transcribe the collected information into the eCRF in English.

5.6.15. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness,
- ***ask each subject's parent(s)/LAR(s) if they are interested to allow the subject to participate in the follow-up study DTPA (BOOSTRIX)-049 BST: 048. Refer to the Section 9.3 for more details. (Amended 06 September 2016)***
- 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 06 September 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 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.

5.7.2. Biological samples

The biological samples are presented in Table 10.

Table 10 Biological samples

Sample type	Quantity	Unit	Timepoint
Blood	2 *	ml	Visit 1
Blood	5 *	ml	Visit 4

* Approximately

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 11).

Table 11 Humoral Immunity (Antibody determination) ***(Amended 06 September 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* or CEVAC
SER	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	NA	IU/ml	***0***.1	GSK Biologicals* or CEVAC
SER	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals* or CEVAC
SER	Bordetella pertussis.Pertactin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals* or CEVAC
SER	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	NA	EU/ml	5	GSK Biologicals* or CEVAC
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 Poliovirus Sabin Type 2 Ab Poliovirus Sabin Type 3 Ab	NEU	NA	ED50	8	GSK Biologicals*
SER	Haemophilus influenzae type b.Polyribosyl Ribitol Phosphate Ab	ELI	NA	µg/ml	***0***.15	GSK Biologicals* or CEVAC
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	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 †
	Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG Streptococcus pneumoniae.Polysaccharide 19A Ab.IgG Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG					
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.
** At the discretion of GSK Biologicals, pneumococcal testing may be done at a GSK Biologicals laboratory or the ***World Health Organisation*** (WHO) reference laboratory.

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*** ***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 = Neutralization assay
CLIA = ChemiLuminescence ImmunoAssay
CEVAC: Centre for Vaccinology, Ghent University and Hospital
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

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 12.

Table 12 Immunological read-outs *(Amended 06 September 2016)*

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

Pre-Pri: Blood sample to be collected before the first dose of the primary vaccination course.
Post-Pri: Blood sample to be collected one month after the last dose of the primary vaccination course, depending on the vaccination schedule.
** Depending on the vaccination schedule*

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). The assay cut-off of ELISA is currently set at 0.1 International Units per ml (IU/ml), which 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. Antibody titres greater than or equal to 1:8 are considered as 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 currently 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 assay. 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 vaccine

The candidate vaccine 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 vaccine are labelled and packed according to applicable regulatory requirements.

Commercial vaccine are assumed to comply with the specifications given in the manufacturer's SPC.

The study vaccines, formulation and presentation is detailed in Table 13.

Table 13 Study vaccines *(Amended 06 September 2016)*

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)=32DU; Aluminium=700µg Al3+	The DTPa-HBV-IPV component is presented as a turbid white suspension in a pre-filled syringe.	0.5 ml *	***2 or*** 3**
	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;	Suspension for injection in a pre-filled syringe	0.5 ml	2 or 3 ***

Treatment name	Vaccines name	Formulation	Presentation	Volume to be administered*	Number of doses
		PS19A=2.2µg CRM197; PS19F=2.2µg CRM197; PS23F=2.2µg CRM197; $AlPO_4$=125µg Al3+			

*After reconstitution
***** In some countries, Infanrix hexa is given as a 2-dose schedule at 2 and 4 months of age or at 3 and 5 months of age. In other countries Infanrix hexa is given as a 3-dose schedule at 2, 4 and 6 months of age or at 2, 3 and 4 months of age as recommended by the routine immunisation programme.***
*** | ***Prevenar 13 is administered at the same schedule as Infanrix hexa except*** in some countries/regions ***with an Infanrix hexa 3-dose schedule where*** *Prevenar 13* is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.
(Amended 06 September 2016)

6.2. Storage and handling of study vaccine

The study vaccine 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 authorized 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 vaccine.

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 vaccine.

6.3. Dosage and administration of study vaccines

The dosage and administration of study vaccines is given in Table 14.

Table 14 Dosage and administration *(Amended 06 September 2016)*

Type of contact and timepoint	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side
Visit 1 (Day 0), Visit 2 (Month 2), Visit 3 (Month 4)* Or Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2)**	0.5 ml	dTpa Group and Control Group	*Infanrix hexa*	IM	T***high***	Right
Visit 1 (Day 0), Visit 2 (Month 2), Visit 3 (Month 4)* Or Visit 1 (Day 0), Visit ***2*** (Month 2)† ***Or Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2****	0.5 ml	dTpa Group and Control Group	*Prevenar 13*	IM	T***high***	Left
Visit 1 (Day 0), Visit 2 (Month 2)*	***0.5 ml***	***dTpa Group and Control Group***	***Infanrix hexa***	***IM***	***Thigh***	***Right***
Visit 1 (Day 0), Visit 2 (Month 2)*	***0.5 ml***	***dTpa Group and Control Group***	***Prevenar 13***	***IM***	***Thigh***	***Left***

[1]Intramuscular (IM)
*For subjects vaccinated with ***Infanrix hexa*** at 2, 4 and 6 months of age
** For subjects vaccinated ***Infanrix hexa*** at 2, 3 and 4 months of age
***** ***For subjects vaccinated with Infanrix hexa at 2 and 4 months of age or at 3 and 5 months of age. These subjects will receive Prevenar 13 at the same vaccination schedule.***
† In some countries/regions ***with an Infanrix hexa 3-dose schedule***, *Prevenar 13* is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects, at least 5% additional vaccine doses will be supplied to replace those that are unusable.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of *Infanrix hexa*. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4).

- Anaphylaxis following the administration of vaccine.
- Hypersensitivity reaction to any component of the vaccine(s) and any excipients in the formulation.

- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Contraindication to *Infanrix hexa*:
  - Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination 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.

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 Table 6 ***to Table 9*** as applicable), or the subject may be withdrawn at the discretion of the investigator (see Section 8.4). ***(Amended 06 September 2016)***

- 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 rectal/axillary.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

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) within 48 hours of vaccination.
  - Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
  - Convulsions with or without fever, occurring within 3 days of vaccination.

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- 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) immunisation 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.
- The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very preterm infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in these infants, vaccination should not be withheld or delayed.
- 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 hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of *Infanrix hexa* and *Prevenar 13*.

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

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit, 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 medications/products/vaccines must be recorded in the eCRF.

- All concomitant medications/products, except vitamins and dietary supplements, administered in the period starting from the first dose of study vaccines (Visit 1) and ending at the last study visit (Visit 4).
- Any concomitant vaccination administered in the period starting from the administration of the first dose of study vaccines (Visit 1) and ending at the last study visit (Visit 4). Note: Medications/vaccinations listed prior to the first dose of study vaccines 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 vaccines used within 30 days preceding the first dose of study vaccines, or planned use during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) since birth. 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/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***me***, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

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

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.
- New conditions detected or diagnosed after investigational vaccine 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 first 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 15 Solicited local adverse events

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

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 16 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 etc) 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, 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 each dose of study vaccine (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 first receipt of study vaccine and will end 30 days following administration of the last dose of study vaccine for each subject. 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 of the first receipt of study vaccine.

SAEs that are related to the investigational vaccine will be collected and recorded from the time of the first receipt of study vaccine until the subject is discharged from the study.

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 subjects' 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 17, Table 18 ***and Table 19***. ***(Amended 06 September 2016)***

Table 17 Reporting periods for adverse events and serious adverse events for subjects vaccinated *with Infanrix hexa* at 2, 4 and 6 months of age (Amended 06 September 2016)

Event	Pre-V1*		V1	3 d post V1	30 d post -V1		V2	3 d post V2	30 d post-V2		V3	3 d post V3	30 d post-V3	V4 Study Conclusion			
			D0		D 30		M2				M 4			M5			
Solicited local and general AEs																	
			■	■			■	■			■	■					
Unsolicited AEs																	
			■	■	■		■	■	■		■	■	■				
AEs/SAEs leading to withdrawal from the study																	
			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs†																	
	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs related to study participation or concurrent GSK medication/ vaccine†																	
	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

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

† AEs/SAEs reported from the administration of first dose of primary vaccination until the end of study will be recorded and analysed in this study (i.e. a part of 201330 [DTPA (BOOSTRIX)-048 PRI] study).

Table 18 Reporting periods for adverse events and serious adverse events for subjects vaccinated *with Infanrix hexa* at 2, 3 and 4 months of age (Amended 06 September 2016)

Event	Pre-V1*		V1	3 d post V1	30 d post -V1		V2	3 d post V2	30 d post-V2		V3	3 d post V3	30 d post-V3	V4 Study Conclusion			
			D0		D 30		M1				M2			M3			
Solicited local and general AEs																	
Unsolicited AEs																	
AEs/SAEs leading to withdrawal from the study																	
SAEs†																	
SAEs related to study participation or concurrent GSK medication/ vaccine†																	

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

† AEs/SAEs reported from the administration of first dose of primary vaccination until the end of study will be recorded and analysed in this study (i.e. a part of 201330 [DTPA (BOOSTRIX)-048 PRI] study).

Table 19 Reporting periods for adverse events and serious adverse events for subjects vaccinated with Infanrix hexa at 2 and 4 months of age or at 3 and 5 months of age (Amended 06 September 2016)

Event	Pre-V1*		V1	3 d post V1	30 d post-V1		V2	3 d post V2	30 d post-V2	V4 Study Conclusion			
			D0		D 30		M2			M3			
Solicited local and general AEs													
Unsolicited AEs													
AEs/SAEs leading to withdrawal from the study													
SAEs†													
SAEs related to study participation or concurrent GSK medication/ vaccine†													

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

† AEs/SAEs reported from the administration of first dose of primary vaccination until the end of study will be recorded and analysed in this study (i.e. a part of 201330 [DTPA (BOOSTRIX)-048 PRI] study).

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 17, Table 18 ***or Table 19 (Amended 06 September 2016)***. 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 20 Intensity scales for solicited symptoms in infants less than 6 years of age

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 rectal/axillary.

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 tympanic route)*** will be scored at GSK Biologicals as follows: ***(Amended 06 September 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 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 to determine his/her assessment.

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 vaccine, 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. 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 in the eCRF.

8.3. Reporting of serious adverse events and other events

8.3.1. Prompt reporting of serious adverse events and other 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 21, once the investigator determines that the event meets the protocol definition of a SAE.

Table 21 Timeframes for submitting serious adverse events 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

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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 21.

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 21).

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 visits/contacts until 30 days after the last 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.
- with other non-serious AEs, until the end of the study period or they are 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 a electronic Expedited Adverse Events Report as applicable.

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).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination 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.
- Other (specify).

9.3. Extension study

At the end of the study (study conclusion visit), the investigator will ask each subject's parent(s)/LAR(s) if they are interested to allow the subject to participate in the follow-up study DTPA (BOOSTRIX)-049 BST: 048. If a subject's parent(s)/LAR(s) are not interested in allowing their child to participate in the follow-up study the reason for refusal will be documented in the subject's eCRF.

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 last dose of primary vaccination.
  - Vaccine response to PT, FHA and PRN antigens, one month after the last dose of primary vaccination.

10.2. Secondary endpoints

- Persistence of antibodies before the first dose of *Infanrix hexa*.
  - Anti-diphtheria and anti-tetanus seroprotection status, anti-PT, anti-FHA, anti-PRN seropositivity status and antibody concentrations.
- Immunogenicity with respect to components of *Infanrix hexa* and *Prevenar 13*.
  - 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, one month after the last dose of primary vaccination.
- Immunogenicity with respect to components of *Infanrix hexa*.
  - Anti-PT, anti-FHA, anti-PRN antibody seropositivity status, one month after the last dose of primary vaccination.
- Solicited local and general symptoms.
  - Occurrence of solicited local/general symptoms during the 4-day (Day 0-Day 3) follow-up period after each vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited symptoms during the 31-day (Day 0-Day 30) follow-up period after each vaccination.
- Serious adverse events.
  - Occurrence of SAEs from first vaccination dose to study end.

10.3. Determination of sample size

The sample size for this study is not derived from any power based calculation. The sample size would consist of all infants whose mothers were enrolled in the study 116945 [DTPA (BOOSTRIX)-047]. Considering approximately 10%-30% reduction in the number of evaluable subjects due to drop-outs and protocol violations from the initial

study, the table below gives the estimated sample size of evaluable subjects that can be expected and the precision achieved with this sample for various expected values.

Table 22 Exact 95% CI of the different values of observed response rate (vaccine response rate or seroprotection rate) for a sample size of 238-300 subjects)

Number of evaluable subjects	Observed response rate expressed as a percentage	Exact 2-sided 95% CI for this observed rate for a sample size of 300 subjects	
		Lower Limit (LL)	Upper Limit (UL)
300	70	64.5	75.1
	75	69.7	79.8
	80	75.0	84.4
	85	80.4	88.8
	92	88.3	94.8
	93	89.5	95.6
	94	90.7	96.4
	95	91.9	97.2
	96	93.1	97.9
	97	94.4	98.6
	98	95.7	99.3
	99	97.1	99.8
	100	98.8	100.0
272	70	64.4	75.6
	75	69.4	80.0
	80	74.9	84.7
	85	80.5	89.3
	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	70	63.9	75.9
	75	69.2	80.6
	80	74.6	85.1
	85	80.1	89.5
	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

Reference study:
217744/070: Group receiving DTPa-HBV-IPV/Hib full-term infants according to 2, 4, 6 schedule in Spain.
217744/078: Group receiving DTPa-HBV-IPV/Hib +Prevenar according to 2, 3, 4 schedule in Germany.

217744/054: Group receiving DTPa-HBV-IPV/Hib according to 3,5,11 schedule in Italy and Germany [Hardy-Fairbanks, 2013]. Based on this reference, the confidence interval of lower response rate also included in case of any immune interference.

The reference values are presented in Table 23.

Table 23 Reference values

Study Group	Schedule (months)	N	D	T	PT VR	FHA VR	PRN VR	HBs	POLIO TYPE 1	POLIO TYPE 2	POLIO TYPE 3	PRP
217744/070												
DTPa-HBV-IPV/Hib pre-term	2,4,6	93	100	100	98.9	100	100	93.4	100	100	100	92.5
DTPa-HBV-IPV/Hib full-term	2,4,6	89	100	100	98.9	100	98.9	95.2	100	100	100	97.8
217744/078												
DTPa-HBV-IPV/Hib	2,3,4	138	100	100	100	97.8	97.8	97.8	100	98.4	99.2	95.7
DTPa-HBV-IPV/Hib + *Prevenar*	2,3,4	141	100	100	98.6	94.8	95.0	97.9	100	99.3	100	93.6
217744/054												
DTPa-HBV-IPV/Hib	3,5,11	177	97.6	99.4	95.9	97.5	98.2	96.4	97.4	94.7	99.3	92.8

N = number of subjects included in the ATP cohort for immunogenicity
D and T: % with antibody concentration ≥ 0.1 IU/ml; HBs: % with antibody concentration ≥10 mIU/ml; polio: % with antibody titre ≥1:8; PRP: % with antibody concentrations ≥0.15µg/ml.
VR= Vaccine response: 1) Pre-vaccination seronegative subjects: appearance of antibodies (concentration ≥cut-off) 2) Pre-vaccination seropositive subjects: post-vaccination concentration≥ pre-vaccination concentration
Pre-term infants (gestation period < 37 weeks)
Full-term infants (gestation period ≥ 37 weeks)

(Amended 06 September 2016)

10.4. Cohorts for analyses

Three cohorts are defined for the purpose of the analysis:

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

10.4.1. Total vaccinated cohort

The TVC will include all vaccinated subjects for whom data are available. ***(Amended 06 September 2016)***

- A safety analysis based on the TVC will include all subjects with at least one vaccine administration documented.
- An immunogenicity analysis based on the TVC will include vaccinated subjects for whom data concerning immunogenicity endpoint measures are available.

10.4.2. ATP 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 at least one dose of study vaccines according to their random assignment.
- 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.

10.4.3. ATP cohort for analysis of immunogenicity

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

- who meet all eligibility criteria;
- who comply with the procedures and intervals defined in the protocol.
- who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 6.7.2) during the study;
- who do not receive a product leading to exclusion from an ATP analysis as listed in Section 6.7.2;
- who do not present with a medical condition leading to exclusion from an ATP analysis as listed in Section 6.8;
- who are born full term (full term is defined ≥ 37 weeks of gestation);

- 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 vaccines antigen component.

The interval between the last vaccination visit and post-primary 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 the laboratory assays section (Section 5.7.1).

- 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 11.
- 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.
- Vaccine response to the PT, FHA and PRN antigens, is defined as:
  - appearance of antibodies in subjects who were initially seronegative (i.e., with concentrations <cut-off value).
  - at least maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e., with concentrations ≥cut-off value).
- 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.

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 4 days post-vaccination, 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 analysis of unsolicited AEs, such as SAEs or AEs by primary Medical Dictionary for Regulatory Activities (MedDRA) term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects, who do not report the event or the concomitant medication, will be considered as subjects without the event or the concomitant medication, respectively.
- For summaries reporting both solicited and unsolicited AEs, all vaccinated subjects will be considered. Subjects, who do not report the event or the concomitant medication, will be considered as subjects without the event or the concomitant medication, respectively.

10.6. Analysis of demographics

Demographic characteristics (age in weeks, race, height [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;
- 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 timepoint 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.

For serology results one month after last vaccination dose:

- The vaccine response rates to PT, FHA and PRN (with exact 95% CI) will be calculated.
- 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.

Additional summaries will be provided based on country.

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 doses and 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] after each vaccine dose and overall. 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 percentage of doses and 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 each 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.
- 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 the 31-day follow-up (Day 0 – Day 30) will be tabulated (with exact 95% CI [Clopper, 1934]) after each vaccine dose and overall.
- SAEs reported from first vaccination dose up to study end will be described in detail.
- Withdrawal due to AEs and SAEs following vaccinations will be described in detail.

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 and SAEs. 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 06 September 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<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.

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

Infanrix hexa and *Prevenar 13* vaccines should be administered to the infants according to the immunisation schedules of the participating countries.

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APPENDIX A CLINICAL LABORATORIES

Table 24 GSK Biologicals' laboratories *(Amended 06 September 2016)*

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

Table 25 Outsourced laboratories *(Amended 06 September 2016)*

Laboratory	Address
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	201330 [DTPA (BOOSTRIX)-048 PRI]
EudraCT number	2014-001117-41
Amendment number:	Amendment 1
Amendment date:	06 September 2016
Co-ordinating authors:	PPD, Lead Scientific Writer and PPD, Scientific Writer

Rationale/background for changes:
Given the fact that only infants born from mothers vaccinated in the previous study (116945 [DTPA (BOOSTRIX)-047) can be enrolled in the current study, the enrolment in DTPA (BOOSTRIX)-047 study has an impact on this current study (e.g. cohorts to be investigated). Initially, the DTPA (BOOSTRIX)-047 study was opened only in countries using 3-dose primary vaccination series against diphtheria, tetanus and pertussis in infants. Nevertheless, the 2-dose primary vaccination schedule 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 therefore the current study to countries using 2-dose primary vaccination series in infants with the aim to increase the scientific value of the study and generate clinical data in diverse infant vaccination schedules.

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

The names and functions of the contributing authors have been updated. The name of GSK Biologicals' Global Vaccines Clinical Laboratories (GVCL) department has been updated to Clinical Laboratory Sciences (CLS) and the name of outsourced laboratory (Quest Diagnostic laboratory is now called Q² Solutions) has also 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 , PPD ***and*** PPD , Project-Level CRDLs

- PPD, PPD ***and*** PPD**,** Study Delivery Leads
- PPD ***and*** ~~GVCL~~ PPD***CLS Study*** ~~Project~~ Managers
- PPD ***and*** PPD**,** Global Clinical Regulatory Affairs Representatives
- PPD, PPD and PPD, Clinical Safety Representatives
- PPD ***and*** PPD Study Data Managers
- PPD***, Project Data Manager***
- PPD ***and*** PPD Senior Managers, Biometrics
- PPD ***and*** PPD ~~,Vaccines Supply Coordinator~~ ***Clinical Trial Supplies Managers***
- ~~PPD , Study Delivery Manager~~
- PPD ***and*** PPD**,** Local Delivery Leads
- PPD ***and*** PPD***, Local Delivery Leads***
- PPD ***and*** PPD, Local Delivery Leads
- PPD***, Local Delivery Lead***
- PPD***, Local Delivery Lead***
- PPD ***and*** PPD***, Local Delivery Leads***

List of Abbreviations: The following changes have been made

CEVAC:	***Centre for Vaccinology, Ghent University and Hospital***
CLS:	***Clinical Laboratory Sciences***
CRDL:	***Clinical Research and Development Lead***
DTP*a*~~--A-~~HBV-IPV/Hib:	Combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b vaccine (*Infanrix hexa*)
EL.U:	***ELISA Units***
EOS	***End of study***
EPAR:	***European Public Assessment Report***
HHE:	***Hypotonic Hyporesponsive Episode***
IM:	***Intramuscular***
IMP:	***Investigational Medicinal Product***
***(m)*IU:**	***(Milli)-***international units
RSI:	***Reference Safety Information***

SCID:	***Severe Combined immunodeficiency Disease***
SDV:	***Source Document Verification***
SIDS:	***Sudden Infant Death Syndrome***
SPM:	***Study Procedures Manual***
SRT	***Safety Review Team***
[e]TDF:	***(electronic) Temperature excursion Decision Form***

Glossary of terms: The definition of End of study (EoS) was added.

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: The following change has been made

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Prevenar 13® (Wyeth Pharmaceuticals Inc.; Marketed by Pfizer Inc.)	***Pneumococcal ~~Pneumoccocal~~*** 13-valent conjugate vaccine (diphtheria CRM_{197} protein)

Synopsis and Section 1.2.1: Rationale for the study:
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~~Tdap~~*** immunisation can decrease the incidence of infant pertussis.

The National Advisory Committee on Immunisation 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~~dTap~~*** vaccination. In special circumstances, such as an outbreak situation, all pregnant women who are of 26 weeks gestation or greater may be offered ***dTpa~~dTap~~*** vaccination irrespective of their immunisation history [Warshawsky, 2014; Public Health Agency of Canada, 2014].

In line with these recommendations, study 116945 [DTPA (BOOSTRIX)-047] will be conducted to evaluate the immunogenicity and safety of GlaxoSmithKline (GSK) Biologicals' dTpa vaccine, *Boostrix*, in pregnant women***, as well as the transfer of maternal antibodies against pertussis to the foetus (cord blood sample at delivery)***. Subjects will receive a dose of *Boostrix* during pregnancy or immediately post-delivery.

Synopsis and Section 1.2.2: Rationale for the study design:
This phase IV study is a follow-up of the study 116945 [DTPA (BOOSTRIX)-047]. The immunogenicity and safety of *Infanrix hexa* when administered as a part of the primary vaccination schedule, ***according to the routine national immunisation schedule (3 doses given at 2, 4 and 6 months of age or at 2, 3 and 4 months of age or 2 doses given at 3 and 5 months of age or at 2 and 4 months of age)*** will be evaluated. ***As part of the study*** subjects will also receive *Prevenar 13* ***according to the routine national immunisation schedule*** ~~as part of the study~~. The immunogenicity and safety of the booster dose of the same vaccines in infants in the second year of their life will be assessed in another follow-up study DTPA (BOOSTRIX)-049.

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. who received a single dose of *Boostrix* during pregnancy and a dose of placebo immediately post-delivery. All infants in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* ***according to the routine national immunisation schedule***.
- Control Group: This group will consist of infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047], i.e. who received a single dose of placebo during pregnancy and a dose of *Boostrix* immediately post-delivery. All infants in this group will receive *Infanrix hexa* co-administered with *Prevenar 13* ***according to the routine national immunisation schedule***.

Section 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/legally acceptable representative(s) [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.

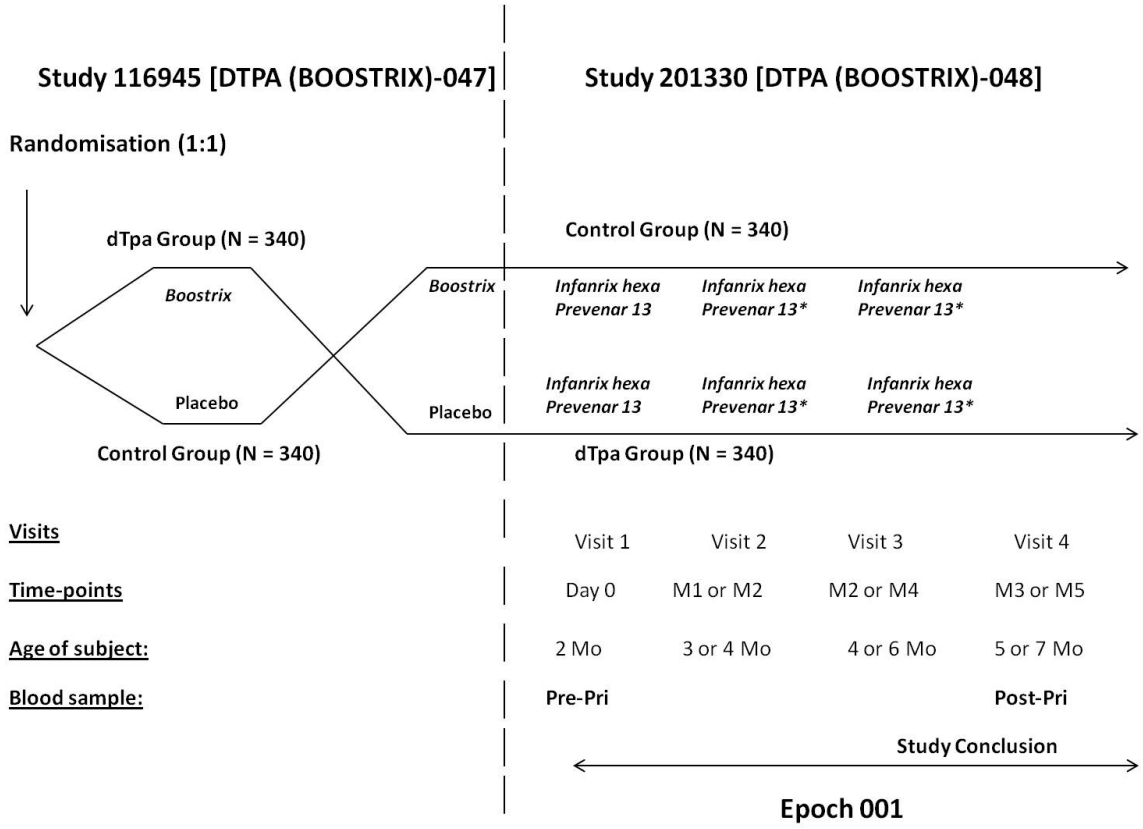
Synopsis and Section 2.2: Secondary objectives

- To assess the safety and reactogenicity of *Infanrix hexa* and *Prevenar 13* in terms of solicited and unsolicited symptoms and serious adverse events (SAEs).

  *In some countries/regions with an ***Infanrix hexa 3-dose vaccination schedule***, *Prevenar 13* ***could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule)*** ~~is administered as 2-dose schedule at 2 and 4 months of age~~. In such an instance, the evaluation will be ***performed one month after the last Infanrix hexa dose regardless of Prevenar 13 vaccination*** ~~schedule2 or 3 months after the last dose of primary vaccination in infants according to the vaccination schedule.~~ ***In the countries/regions with an Infanrix hexa 2-dose schedule, Prevenar 13 is co-administered at the same time as Infanrix hexa.***

Synopsis and Section 3. Study Design Overview

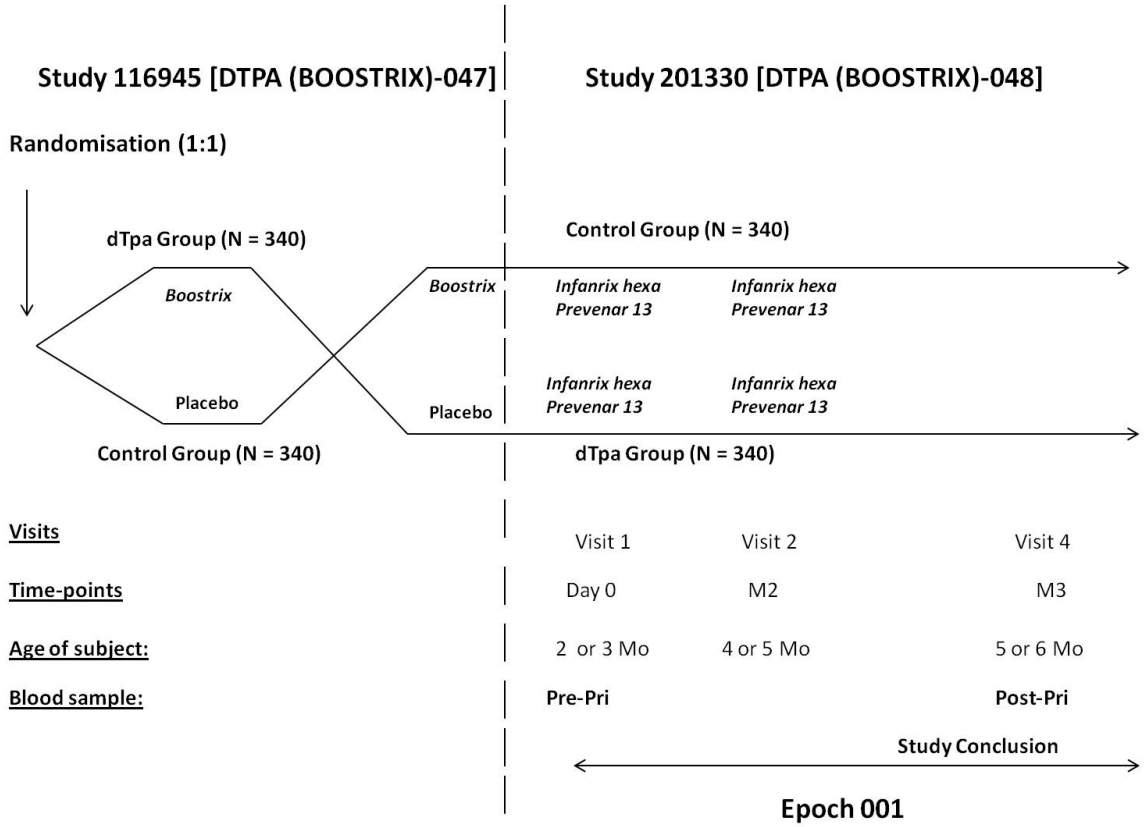
Figure 1: Study design diagram for infants receiving a 3-dose schedule of Infanrix hexa



N: Maximum number of subjects planned to be enrolled
M = Month, Mo = age in months

Timepoints have been numbered based on the different vaccination schedules. D0, M1, M2 and M3 timepoints reflect for subjects who will be vaccinated according to the 2, 3 and 4 month schedule while D0, M2, M4 and M5 timepoints reflect for subjects who will be vaccinated according to the 2, 4 and 6 month schedule.
* In some countries/regions ***with an Infanrix hexa 3-dose schedule***, *Prevenar 13* is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.
Pre-Pri = Blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = Blood sample to be collected one month after the last dose of the primary vaccination course

Figure 2: Study design diagram for infants receiving a 2-dose schedule of Infanrix hexa



N: Maximum number of subjects planned to be enrolled
M = Month, Mo = age in months
Pre-Pri = Blood sample to be collected before the first dose of the primary vaccination course
Post-Pri = Blood sample to be collected one month after the last dose of the primary vaccination course
Subjects will be vaccinated either at 2 and 4 months of age or 3 and 5 months of age, according to the routine national immunisation schedule

- Duration of the study: The intended duration of the study is approximately 3 months, per subject, for subjects vaccinated according to ***the 2 and 4, the 3 and 5 or*** the 2, 3 and 4 months schedule and approximately 5 months, per subject, for those vaccinated according to 2, 4 and 6 month schedule.

  Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 4 (Month ***3 or*** 5***, depending on the vaccination schedule).***

- ***End of Study (EoS): Last testing results released of samples collected at Visit 4.***

Table 1: Study groups and epoch foreseen in the study

Study Groups	Number of subjects	Age (Min - Max)*	Epoch
			Epoch 001
dTpa Group	340	6 -***14*** weeks	x
Control Group	340	6 -***14*** weeks	x

*Up to ***and including 14 weeks and 6 days of age***~~but not including 12 weeks of age~~.

Table 2: Study groups and treatments foreseen in the study

Treatment names	Vaccine name	Study Groups	
		dTpa Group	Control Group
Infanrix hexa	DTP~~a~~A-HBV-IPV	x	x

- Vaccination schedules: All subjects will receive ***either 3 doses of*** *Infanrix hexa* co-administered with *Prevenar 13** at 2, 4 and 6 months or 2, 3 and 4 months, ***either 2 doses of Infanrix hexa co-administered with Prevenar 13 at 3 and 5 months or 2 and 4 months,*** depending on the immunisation schedule of the country.

  *In some countries/regions ***with an Infanrix hexa 3 doses routine national immunisation schedule***, *Prevenar 13* ***could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule)***~~is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.~~

- Blinding: Open-label. Note: The study personnel operating GSK Biologicals' randomisation system on internet (SBIR) and the site staff will remain blinded towards the treatment allocation to subjects in study 116945 [DTPA (BOOSTRIX)-047] ~~and study 201330 [DTPA (BOOSTRIX)-048 PRI]~~.

- Sampling schedule: Blood samples will be drawn from all subjects at the following timepoints:

  – Pre-Pri: Before ***the first Infanrix hexa*** vaccine administration, a volume of approximately 2 mL of whole blood (to provide approximately 0.7 mL of serum) will be collected ***from all study participants***.

  – Post-Pri: One month after the last ***dose of Infanrix hexa*** ~~dose of~~ primary vaccination, approximately 5 mL of whole blood (to provide approximately 1.7 mL of serum) will be collected ***from all study participants***.

  – Safety monitoring: An independent data monitoring committee (IDMC) (including paediatrician and statistician) will be put in place to oversee the safety of infants born to mothers who were vaccinated with *Boostrix* during pregnancy in the clinical study 116945 [DTPA (BOOSTRIX)-047] i.e. each SAE/incidence of grade 3 local and general solicited AE~~e~~s, unsolicited AEs will be reviewed by this committee ***as per IDMC approved charter***.

Synopsis and Section 4.1: Number of Subjects/centers

A maximum of 680 infants aged 6-*14*~~12~~ weeks (up to ***and including 14 weeks and 6 days of age*** ~~but not including 12 weeks~~) 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 terminated when all the eligible infants born to ***pregnant women***~~subjects~~ from the 116945 [DTPA (BOOSTRIX)-047] study are enrolled.

Section 4.2: Inclusion criteria for enrolment

- A male or female between, 6 and 14 weeks of age (including 6 weeks and up to ~~but not including 14 weeks~~ ***and including 14 weeks and 6 days of age***) at the time of the first vaccination.

Section 5.2.2.1.1:Study group and treatment number allocation

The target will be to enrol maximum of 680 eligible subjects aged 6-***14***~~12~~ weeks (up to ***and including 14 weeks and 6 days of age*** ~~but not including 12 weeks~~) (approximately 340 subjects in each group).

Section 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 to subjects in study 116945 [DTPA (BOOSTRIX)-047] ~~and study 201330 [DTPA (BOOSTRIX)-048 PRI]~~.

Section 5.4.1: Independent Data Monitoring Committee

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 ***and*** unsolicited AEs at specified times and access to data on request by an unblinded statistician.

Section 5.4.2: Responsibilities

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 ~~Charter~~***charter***. 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 ***and*** unsolicited AEs), provide

06-SEP-2016 103

GSK Biologicals with indications on safety profiles and make recommendations for consultation of regulatory authorities and on further study conduct.

Section 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.

Section 5.4.4: GSK Biologicals' safety review team

A***t GSK Biologicals, a*** Safety Review Team ***(SRT) will*** includ~~eing~~ the Central Safety Physician, the ***Clinical Research and Development Lead (***CRDL) and Biostatistician of the project as well as Epidemiology and Regulatory representative. ***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 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.

Section 5.5: Outline of Study Procedures

The list of study procedures ***for infants receiving a 3-dose and a 2-dose schedule of Infanrix hexa*** is detailed below in Table 4 ***and Table 5, respectively***.

Table 4: List of study procedures for infants receiving a 3-dose schedule of Infanrix hexa

Age	2 months	3 or 4 months	4 or 6 months	5 or 7 months
Epoch	Epoch 001			
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4
Timepoints	Day 0	Month 1 or 2#	Month 2 or 4#	Month 3 or 5#
Sampling timepoints	Pre-Pri			Post-Pri
Record pre-vaccination body temperature	●	●	●	
Recording of ~~serious adverse events~~ (SAEs~~)~~	●	●	●	●

** In some countries/regions ***with an Infanrix hexa 3-dose schedule***, *Prevenar 13* is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.

Table 5: List of study procedures for infants receiving a 2-dose schedule of Infanrix hexa

Age	*2 or 3 months#*	*4 or 5 months#*		*5 or 6 months#*
Epoch	*Epoch 001*			
Type of contact	*Visit 1*	*Visit 2*	*Visit 3***	*Visit 4*
Timepoints	*Day 0*	*Month 2*		*Month 3*
Sampling timepoints	*Pre-Pri*			*Post-Pri*
Informed consent	●			
Check inclusion/exclusion criteria	●			
Collect demographic data	●			
*Medical history, including medication/vaccine history**	●			
History directed physical examination	●			
Check contraindications and warnings and precautions	*O*	*O*		
Record pre-vaccination body temperature	●	●		
Record body weight, height and head circumference	●			●
Study group and treatment number allocation	●			
Treatment number allocation for subsequent doses		*O*		
Recording of administered treatment number	●	●		
Blood sampling for antibody determination	●			●
Vaccine administration	●	●		
Record any concomitant medication/vaccination	●	●		●
Record any intercurrent medical conditions		●		●
Distribution of diary cards	*O*	*O*		
Recording of solicited adverse events (Day 0- Day 3) by subjects' parent(s)/LAR(s)	●	●		
Recording of non-serious adverse events (Day 0- Day 30) by subjects' parent(s)/LAR(s)	●	●		●
Return of diary cards		*O*		*O*
Diary card transcription by investigator or site staff		●		●
Recording of SAEs	●	●		●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●		●
Withdrawals due to AEs/SAEs	●	●		●
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.
Pre-Pri: Blood sample to be collected before the first dose of the primary vaccination course (~2 mL).
Post-Pri: Blood sample to be collected one month after the last dose of the primary vaccination course (~5 mL).
 # Depending on the immunisation schedule of the country.
** History of all medications given to the infants will be recorded in the eCRF.*
*** Subject receiving 2 doses of Infanrix hexa will not attend the Visit 3*

The intervals between study visits for subjects ***receiving 3 doses of Infanrix hexa***~~vaccinated~~ at 2, 4 and 6 months and 2, 3 and 4 months are presented in Table 6 and Table 7, respectively. ***the intervals between study visits for subjects receiving 2 doses of Infanrix hexa at 2 and 4 months and at 3 and 5 months are presented in Table 8 and Table 9, respectively.***

Table 6: Intervals between study visits for subjects vaccinated *with Infanrix hexa* at 2, 4 and 6 months of age

Interval	Optimal length of interval [1]	Allowed interval[2†]
Birth →Visit 1	60 days	42-~~83~~***104*** days

Table 7: Intervals between study visits for subjects vaccinated *with Infanrix hexa* at 2, 3 and 4 months of age

Interval	Optimal length of interval [1]	Allowed interval[2†]
Birth→Visit 1	60 days	42-~~83~~***104*** days

Table 8:Intervals between study visits for subjects vaccinated with Infanrix hexa at 2 and 4 months of age

Interval	*Optimal length of interval [1]*	*Allowed interval[2†]*
Birth →Visit 1	***60 days***	***42-104 days***
Visit 1→Visit 2	***60 days***	***52-78 days***
Visit 2→Visit 4*	***30 days****	***21-48 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.
† Date of previous visit/contact is the reference date
****If subjects return for the visits 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.***
***** Subject receiving 2 doses of Infanrix hexa will not attend the Visit 3***

Table 9: Intervals between study visits for subjects vaccinated with Infanrix hexa at 3 and 5 months of age

Interval	*Optimal length of interval [1]*	*Allowed interval[2†]*
Birth →Visit 1	***90 days***	***42-104 days***
Visit 1→Visit 2	***60 days***	***52-78 days***
Visit 2→Visit 4*	***30 days****	***21-48 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.
† Date of previous visit/contact is the reference date
****If subjects return for the visits 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.***
***** Subject receiving 2 doses of Infanrix hexa will not attend the Visit 3***

Section 5.6.1: Informed consent

Note: At ***Visit 4***, parent(s)/LAR(s) will be informed about the booster follow-up study DTPA (BOOSTRIX)-049 BST: 048 in which their infants will receive a booster dose of the study vaccines ***according to the national immunisation programme***~~during their second year of life. If they allow their child/ward to participate in the follow-up study, they will be contacted when the subject is approximately 9 months of age to complete~~ a

~~standardised developmental screening tool, Ages and Stages Questionnaire-3 either through a secure, Internet-based system that provides automated scoring, or via a paper questionnaire and submit it to the centralised research coordinating centre or the site where the study will be conducted. A separate signed/witnessed/thumb printed informed consent of the subject's parent(s)/LAR(s) for this procedure will be obtained after the completion of all study related activities of this study (i.e this informed consent process will be a part of DTPA (BOOSTRIX)-049 BST: 048 study).~~

Section 5.6.9: Record body weight, height and~~ding~~ head circumference

Section 5.6.11.1: Blood sampling for immune response assessments

- Pre-Pri: Before ***the first Infanrix hexa*** vaccine administration~~at Visit 1~~, a volume of approximately 2 mL of whole blood (to provide approximately 0.7 mL of serum) will be collected.
- Post-Pri: One month after the last ***dose of Infanrix hexa*** ~~dose of~~ primary vaccination at Visit 4, 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 ***and laboratory manual*** for more details on sample storage conditions.

Section 5.6.12: Study ~~Vaccine~~ vaccine administration

- After completing all prerequisite procedures prior to vaccination, study vaccines will be administered intramuscularly (IM) in ***the ~~deltoid of the~~ thigh*** as described in Section 6.3. If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccination, the visit will be rescheduled within the allowed interval for this visit (see Table 6 ***to Table 9,***~~and Table 6~~ as applicable).

Section 5.6.14: Recording of AEs and SAEs

- Collect and verify completed diary cards during discussion with the subject's parent(s)/LAR(s) at ***the next visit***~~Visits 2, 3 and 4~~.

Section 5.6.15: Study conclusion

The investigator will:

- ***ask each subject's parent(s)/LAR(s) if they are interested to allow the subject to participate in the follow-up study DTPA (BOOSTRIX)-049 BST: 048. Refer to the Section 9.3 for more details.***

Section 5.7: Biological sample handling and analysis

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

Section 5.7.3: Laboratory assays

Table 11: 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* or CEVAC
SER	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	NA	IU/ml	***0***.1	GSK Biologicals* or CEVAC
SER	Haemophilus influenzae type b.Polyribosyl Ribitol Phosphate Ab	ELI	NA	µg/ml	***0***.15	GSK Biologicals* or CEVAC
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	ELIF or multiplex	NA	µg/ml	***0***.05 or equivalent cut-off for the multiplex	GSK Biologicals*
SER	Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG	ELI	NA	µg/ml	***0***.15	WHO reference laboratory**

System	Component	Method	Kit / Manufacturer	Unit	Cut-off***	Laboratory †
	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					

*GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences (CLS)***~~Global Vaccines Clinical Laboratories (GVCL)~~ in Rixensart, Belgium; Wavre, Belgium; ~~Laval, Canada.~~

** At the discretion of GSK Biologicals, pneumococcal testing may be done at a GSK Biologicals laboratory or the ***World Health Organisation*** (WHO) reference laboratory.

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

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Table 12: Immunological read-outs

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

**** Depending on the vaccination schedule***

Table 13: 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)=32DU; Aluminium=700µg Al3+	The DTPa-HBV-IPV component is presented as a turbid white suspension in a pre-filled syringe.	0.5 ml *	***2 or*** 3**
	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	2 or 3 ***

*After reconstitution

***** In some countries, Infanrix hexa is given as a 2-dose schedule at 2 and 4 months of age or at 3 and 5 months of age. In other countries Infanrix hexa is given as a 3-dose schedule at 2, 4 and 6 months of age or at 2, 3 and 4 months of age as recommended by the routine immunisation programme.***

******¶| Prevenar 13 is administered at the same schedule as Infanrix hexa except*** in some countries/regions ***with an Infanrix hexa 3-dose schedule where*** *Prevenar 13* is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.

Table 14: Dosage and administration

Type of contact and timepoint	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side
Visit 1 (Day 0), Visit 2 (Month 2), Visit 3 (Month 4)* Or Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2)**	0.5 ml	dTpa Group and Control Group	*Infanrix hexa*	IM	T***high***	Right
Visit 1 (Day 0), Visit 2 (Month 2), Visit 3 (Month 4)* Or Visit 1 (Day 0), Visit ~~3~~***2*** (Month 2)† ***Or Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2*******	0.5 ml	dTpa Group and Control Group	*Prevenar 13*	IM	T***high***	Left
Visit 1 (Day 0), Visit 2 (Month 2)***	***0.5 ml***	***dTpa Group and Control Group***	***Infanrix hexa***	***IM***	***Thigh***	***Right***
Visit 1 (Day 0), Visit 2 (Month 2)***	***0.5 ml***	***dTpa Group and Control Group***	***Prevenar 13***	***IM***	***Thigh***	***Left***

[1]Intramuscular (IM)
[2]~~Thigh (T),~~
*For subjects vaccinated with ***Infanrix hexa*** at 2, 4 and 6 months of age
** For subjects vaccinated ***Infanrix hexa*** at 2, 3 and 4 months of age
****** For subjects vaccinated with Infanrix hexa at 2 and 4 months of age or at 3 and 5 months of age. These subjects will receive Prevenar 13 at the same vaccination schedule.***
† In some countries/regions ***with an Infanrix hexa 3-dose schedule***, *Prevenar 13* is given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.

Section 6.5: Contraindications to subsequent vaccination

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 Table 6 ***to Table 9***~~and Table 7~~ as applicable), or the subject may be withdrawn at the discretion of the investigator (see Section 8.4).

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

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***me***, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

Section 8.1.2: Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

d. Results in disability/incapacity~~, OR~~

Section 8.2.1: Time period for detecting and recording adverse events and serious adverse events

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 17, ~~and~~ Table 18 ***and Table 19***.

Table 17: Reporting periods for adverse events and serious adverse events for subjects vaccinated *with Infanrix hexa* at 2, 4 and 6 months of age

Table 18: Reporting periods for adverse events and serious adverse events for subjects vaccinated *with Infanrix hexa* at 2, 3 and 4 months of age

Table 19: Reporting periods for adverse events and serious adverse events for subjects vaccinated with Infanrix hexa at 2 and 4 months of age or at 3 and 5 months of age

Event	Pre-V1*		V1	3 d post V1	30 d post-V1		V2	3 d post V2	30 d post-V2	V4 Study Conclusion			
			D0		D 30		M2			M3			
Solicited local and general AEs													
Unsolicited AEs													
AEs/SAEs leading to withdrawal from the study													
SAEs†													
SAEs related to study participation or concurrent GSK medication/ vaccine†													

**** i.e. consent obtained. Pre-V: pre-vaccination; V: vaccination; Post-V: post-vaccination; D: Day, M: Month***
† AEs/SAEs reported from the administration of first dose of primary vaccination until the end of study will be recorded and analysed in this study (i.e. a part of 201330 [DTPA (BOOSTRIX)-048 PRI] study).

Section 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 17, ~~or~~ Table 18 ***or Table 19***. 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.

Section 8.2.3.2.1: Assessment of intensity

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

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

Section 10.3: Determination of sample size

Table 23: Reference values

Study Group	Schedule (months)	N	D	T	PT VR	FHA VR	PRN VR	HBs	POLIO TYPE 1	POLIO TYPE 2	POLIO TYPE 3	PRP
DTPa-HBV-IPV/Hib	3,5,11	177	~~100~~***97.6***	~~100~~***99.4***	~~100~~***95.9***	~~100~~***97.5***	~~100~~***98.2***	~~100~~***96.4***	~~100~~***97.4***	~~100~~***94.7***	~~100~~***99.3***	~~100~~***92.8***

Section 10.4: Cohorts for ~~a~~Analyses

Section 10.4.1: Total vaccinated cohort

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

Section 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 6 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 24: GSK Biologicals' laboratories

Laboratory	Address
~~GSK Biologicals Global Vaccine Clinical Laboratory, North America- Laval~~	~~Biospecimen Reception - Clinical Serology 525 Cartier blvd West - Laval - Quebec - Canada - H7V 3S8~~
GSK Biologicals ~~Global Vaccine Clinical Laboratory~~ ***Clinical Sciences Laboratory***, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals ~~Global Vaccine Clinical Laboratory~~ ***Clinical Sciences Laboratory***, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 25: Outsourced laboratories

Laboratory	Address
Q² Solutions ~~Quest diagnostics Limited Clinical Trials~~ (UK)	***The Alba Campus Rosebank Livingston West Lothian, EH54 7EG Scotland, UK~~Unit B1, Parkway West Industrial Estate Cranford Lane – Heston, Middlesex TW5 9QA UK~~***
Q² Solutions~~Quest Diagnostics~~ Nichols Institute	33608 Ortega Highway San Juan Capistrano, CA 92675-2042 USA

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	201330 [DTPA (BOOSTRIX)-048 PRI]
EudraCT number	2014-001117-41
Date of protocol amendment	Amendment 1 Final: 06 September 2016
Detailed Title	A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety oflnfanrix hexa™ administered as primary vaccination in healthy infants born to mothers given Boostrix™ during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-04 7].
Sponsor signatory	Narcisa Mesaros, MD Clinical and Epidemiology R&D Project Leader (CEPL), DTP, Polio, Hib containing vaccines
Signature	
Date	9 Sept 2016