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

| | |
|---|---|
| **Primary Study vaccine and number** | GlaxoSmithKline (GSK) Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis vaccine (dTpa), *Boostrix* (263855). |
| **eTrack study number and Abbreviated Title** | 201532 [DTPA (BOOSTRIX)-050] |
| **Investigational New Drug (IND) number** | BB-IND-8461 |
| **EudraCT number** | 2015-003405-42 |
| **Date of protocol** | Final Version 01: 21 January 2016 |
| **Date of protocol amendment** | Amendment 01 Final: 02 February 2017<br>Amendment 02 Final: 07 August 2017<br>Amendment 03 Final: 31 October 2017 |
| **Title** | Evaluation of immunogenicity, safety and reactogenicity of GSK Biologicals' dTpa booster vaccine (263855) (*Boostrix*) administered as a booster dose in healthy Russian subjects. |
| **Detailed Title** | A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, *Boostrix*, administered as a booster dose in healthy Russian subjects aged four years and older. |
| **Co-ordinating authors** | PPD, Scientific Writer, contractor for GSK Biologicals and PPD, Scientific Writer |
| **Contributing authors** | • PPD, Clinical and Epidemiology Project Leader<br>• PPD, Clinical Research and Development Lead, contractor for GSK Biologicals<br>• PPD, Clinical Research and Development Lead<br>• PPD/PPD, Lead Statistician<br>• PPD, Project Statistician<br>• PPD/PPD, Study Delivery Lead |

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| **Contributing authors (continued)** | • PPD, Study Delivery Manager<br>• PPD, Head of Clinical Operations, Vaccines<br>• PPD, Senior Clinical Research Associate, Vaccines<br>• PPD, contractor for GSK Biologicals/PPD, Clinical Trial Supply Manager<br>• PPD/PPD, Clinical Read-out Team Leader<br>• PPD/PPD, Business and Decision Life Sciences contractor for GSK Biologicals.<br>• PPD, Project Data Manager<br>• PPD and PPD/PPD, Study Data Manager<br>• PPD, Oversight Data Manager<br>• PPD/PPD, Global Patents Representative<br>• PPD and PPD/PPD and PPD, Clinical Safety Representatives<br>• PPD, Senior Regional Medical Manager<br>• PPD/PPD, Global Regulatory Affairs |

# Protocol Amendment 3 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 201532 [DTPA (BOOSTRIX)-050] |
| **IND number** | BB-IND-8461 |
| **EudraCT number** | 2015-003405-42 |
| **Date of protocol amendment** | Amendment 3 Final: 31 October 2017 |
| **Detailed Title** | A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, *Boostrix*, administered as a booster dose in healthy Russian subjects aged four years and older. |
| **Sponsor signatory** | _____ |
| **Signature** | _____ |
| **Date** | _____ |

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# Protocol Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 201532 [DTPA (BOOSTRIX)-050] |
| **IND number** | BB-IND-8461 |
| **EudraCT number** | 2015-003405-42 |
| **Date of protocol** | Final Version 02: 21 January 2016 |
| **Detailed Title** | A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, Boostrix™, administered as a booster dose in healthy Russian subjects aged three years and older. |
| **Sponsor signatory** | Narcisa Elena Mesaros, MD,<br>Project Level Clinical Research & Development Lead, Clinical Development, Combination Vaccines, Vaccines Discovery and Development, GlaxoSmithKline Biologicals |
| **Signature** | PPD |
| **Date** | 2 Feb 2016 |

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# Protocol Amendment 3 Rationale

| **Amendment number:** Amendment 3 |
|---|
| **Rationale/background for changes:**<br>This protocol amendment was developed in order to accommodate older adults (approximately 58 years old and older) who were born before national recommendations in Russia for infant DTP vaccination, as well as those born when DTP vaccination coverage was low. The protocol amendment would also clarify inconsistencies present in the Protocol Amendment 2, between the English version and the Russian version. Following which, adjustments to the text were made in the inclusion criteria to clarify the enrolment of subjects for age group eight years and above. The wording parent(s)/adoptive parent(s) were aligned according to the local regulations. References for laboratory assays were updated and certain sections were modified to align with the rest of the document. |

# Protocol Amendment 3 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' study 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 ***parent(s)/adoptive parent*(s) (Amended 31 October 2017).**
- 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** | 201532 [DTPA (BOOSTRIX)-050] |
| **IND number** | BB-IND-8461 |
| **EudraCT number** | 2015-003405-42 |
| **Date of protocol amendment** | Amendment 3 Final: 31 October 2017 |
| **Detailed Title** | A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, *Boostrix*, administered as a booster dose in healthy Russian subjects aged four years and older. |
| **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 8.4.2**.**

# SYNOPSIS

| | |
|---|---|
| **Detailed Title** | A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, *Boostrix*, administered as a booster dose in healthy Russian subjects aged four years and older. |
| **Indication** | Booster immunisation against diphtheria, tetanus and pertussis diseases of individuals from age of four years onwards. The study population for this study will include individuals aged four years and older. |
| **Rationale for the study and study design** | • Rationale for the study<br><br>In Russia, DTP vaccines have been indicated for active immunisation against diphtheria, tetanus and pertussis diseases in infants starting at the age of three months. Recent data shows that the coverage rate for DTP vaccine is 97% in Russia [WHO, 2015a]. However, like many developing countries, the DTP vaccination programme does not include older children, adolescents or adults and it is likely that a majority of the population will remain unprotected against such diseases in the future.<br><br>According to the World Health Organization (WHO), the incidence of pertussis disease in Russia was estimated at about 4,705 cases per 100,000 population in 2014 [WHO, 2015b]. Studies have shown that childhood pertussis burden can be significantly reduced by vaccination of adolescents and adults [Ward, 2005; Ward, 2006]. Hence, boosting with reduced-antigen-content diphtheria and tetanus toxoids and acellular pertussis vaccine (dTpa) instead of dT may prolong the immunity against pertussis infection. GlaxoSmithKline (GSK) Biologicals has developed a dTpa vaccine for booster vaccination of children, adolescents and adults against diphtheria, tetanus and pertussis diseases, known as *Boostrix*.<br><br>*Boostrix* vaccine contains 0.5 mg Al (as aluminium phosphate and aluminium hydroxide) per 0.5 millilitre (ml) dose. *Boostrix* is currently not registered in Russia. This study will assess the immunogenicity, reactogenicity and safety of *Boostrix* in healthy Russian subjects aged four years and older. The data obtained from this study will be used to support the registration of *Boostrix* in Russia for individuals aged four years and older.<br><br>• Rationale for the study design<br><br>The study is designed as an open-label, single group trial in which all the study subjects will receive a single dose of |

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

Pertussis outbreaks have occurred in a number of European and non-European countries. This resurgence is observed across the age range with a notable increase in cases now being detected in adolescents and older age groups. It is also now recognized that immunity following either natural pertussis infection or vaccination is not long lived, and the acellular pertussis vaccines that have been widely used since the 1990s may be more prone to such waning. Consequently, adults and adolescents with pertussis are a potential source of infection for infants too young to have been fully vaccinated. Many countries recommend 'cocoon ' strategy, i.e. vaccination of family members and close contact of newborn (i.e. grandparents usually above 65 years old), in order to protect infants from acquiring pertussis. The ≥65 years (elderly population) have therefore been included in the study.

**Objective**

**Primary**

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

**Secondary**

- To assess the immune response in terms of booster response to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.
- To assess the immune response in terms of antibody concentrations to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.
- To assess the reactogenicity and safety of *Boostrix* in terms of solicited symptoms (local and general), unsolicited adverse events (AEs) and serious adverse events (SAEs).

**Study design**

- Experimental design: Phase III, open-label, non-randomised, multi-centric, single-country study with a single group.
- Duration of the study:
  - Epoch 001: Primary Epoch starting at Visit 1 (Day 1)

and ending at Visit 2 (Day 31)

- Primary Completion Date (PCD): Visit 2 (Day 31)
- End of Study (EoS): Last testing results released of samples collected at Visit 2

Study groups: dTpa group: Subjects aged four years and older

**Synopsis Table 1 Study groups and epochs foreseen in the study**

| Study Groups | Number of subjects | Age (Min) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| dTpa Group | 448 | ≥4 years | x |

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

| Treatment name | Vaccine name | Study Groups |
|---|---|---|
| | | dTpa group |
| *Boostrix* | dTpa | x |

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

**Synopsis Table 3 Blinding of study epochs**

| Study Epoch | Blinding |
|---|---|
| Epoch 001 | Open |

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

**Number of subjects** Approximately 448 subjects aged four years and older will be enrolled in the study.

**Endpoints**

**Primary**

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria* and anti-tetanus seroprotection status, one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN seropositivity status, one month after vaccination.

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

**Secondary**

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

*Refer to section 10.5 for the definition of booster response.

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

# TABLE OF CONTENTS

**PAGE**

## LIST OF TABLES

**PAGE**

## LIST OF APPENDICES

**PAGE**

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE:** | Adverse Event |
| **Al:** | Aluminium |
| **ATEAM:** | Appropriate (electronic) temperature excursion decision form |
| **CI:** | Confidence Interval |
| **CLS:** | Clinical Laboratory Sciences |
| **dT:** | Reduced-antigen-content diphtheria and tetanus toxoid vaccine |
| **DTPa:** | Diphtheria, Tetanus, acellular Pertussis Vaccine |
| **dTpa:** | reduced-antigen-content diphtheria and tetanus toxoids and acellular pertussis vaccine |
| **eCRF:** | electronic Case Report Form |
| **EoS:** | End of Study |
| **ELISA:** | Enzyme-linked immunosorbent assay |
| **FHA:** | Filamentous Haemagglutinin |
| **GMC:** | Geometric Mean Concentration |
| **GSK:** | GlaxoSmithKline |
| **IAF:** | Inform Assent Form |
| **IB** | Investigator Brochure |
| **ICF:** | Inform Consent Form |
| **ICH:** | International Conference on Harmonisation |
| **IEC:** | Independent Ethics Committee |
| **IMP:** | Investigational Medicinal Product |
| **IM:** | Intramuscular |
| **IND:** | Investigational New Drug |
| **IRB:** | Institutional Review Board |
| **IU:** | International Unit(s) |
| **MedDRA:** | Medical Dictionary for Regulatory Activities |
| **ml:** | millilitre |
| **PCD:** | Primary Completion Date |
| **PRN:** | Pertactin |
| **PP:** | Per Protocol |
| **PT:** | Pertussis Toxoid |

| | |
|---|---|
| **RDE:** | Remote Data Entry |
| **RSI:** | Reference Safety Information |
| **SAE:** | Serious Adverse Event |
| **SBIR:** | Randomisation System on Internet |
| **SDV:** | Source Document Verification |
| **SmPC:** | Summary of Product Characteristics |
| **SPM:** | Study Procedures Manual |
| **Td:** | Combined tetanus and diphtheria vaccine |
| **TVC:** | Total Vaccinated Cohort |
| **WHO:** | World Health Organization |

# GLOSSARY OF TERMS

**Adequate contraception:** Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- combined estrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

**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. |
| **Eligible:** | Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria. |
| **End of Study**<br>**(Synonym of End of Trial):** | For studies without collection of human biological samples or imaging data EoS is the Last Subject Last Visit (LSLV).<br>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 set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch.<br>Typical examples of epochs are screening 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 per protocol analysis (see Sections 6.7.2 and 10.4 for details on criteria for evaluability). |
| **Immunological correlate of protection:** | The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent. |
| **Investigational vaccine (Synonym of Investigational Medicinal Product):** | A pharmaceutical form of an active ingredient being tested 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. |
| **Menarche:** | Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue). |
| **Menopause:** | Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after one year without menses with an appropriate clinical profile at the appropriate age e.g. >45 years. |
| **Primary completion date**: | The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated. |
| **Protocol amendment:** | The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study. |
| **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 after study vaccine use from the subject or an observer during a specified post-vaccination follow-up period. |
| **Study vaccine:** | Any investigational vaccine being tested and/or any authorised use of a vaccine as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine. |
| **Subject:** | Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control. |
| **Subject number:** | A unique number identifying a subject, assigned to each subject consenting to participate in the study. |
| **Treatment:** | Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject. |
| **Treatment number:** | A number identifying a treatment to a subject, according to 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 trademark is used in the present protocol.**

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

| Trademark of the GSK group of companies | Generic description |
|---|---|
| *Boostrix* | Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (dTpa) vaccine |

# 1. INTRODUCTION

## 1.1. Background

Universal immunisation of infants with multiple doses of paediatric diphtheria and tetanus toxoids and acellular pertussis (DTPa) vaccine, followed by a booster vaccination in the second year of life, and at school age is widely practised worldwide and has controlled the occurrence of diphtheria, tetanus and pertussis in infants. *Boostrix* is a vaccine indicated for active booster immunisation against tetanus, diphtheria, and pertussis. It is approved for use in the European Union as a single dose in individuals four years of age and older.

Pertussis (whooping cough) is a highly infectious respiratory disease caused by *Bordetella pertussis* bacterium. The most common complication seen in young infants for pertussis-related deaths is secondary bacterial pneumonia [CDC, 2015a]. Worldwide, around 16 million cases of pertussis [CDC, 2015b] and about 195,000 deaths per year have been reported [CDC, 2015a]. Pertussis continues to be a serious problem among unvaccinated or incompletely vaccinated infants [Forsyth, 2015]. As the vaccine-induced immunity to pertussis wanes with time, adolescents and adults may serve as a source of infection for neonates and infants too young to be immunised [de Greeff, 2010; Kowalzik, 2007].

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

## 1.2. Rationale for the study and study design

### 1.2.1. Rationale for the study

In Russia, DTP vaccines have been indicated for active immunisation against diphtheria, tetanus and pertussis diseases in infants starting at the age of three months. Recent data shows that the coverage rate for DTP vaccine is 97% in Russia [WHO, 2015a]. However, like many developing countries, the DTP vaccination programme does not include older children, adolescents or adults, and it is likely that a majority of the population will remain unprotected against such diseases in the future.

According to the World Health Organization (WHO), the incidence of pertussis disease in Russia was estimated at about 4,705 cases per 100,000 population in 2014 [WHO, 2015b]. Studies have shown that childhood pertussis burden can be significantly reduced by vaccination of adolescents and adults [Ward, 2005; Ward, 2006]. Hence, boosting with reduced-antigen-content diphtheria and tetanus toxoids and acellular pertussis vaccine (dTpa) instead of diphtheria and tetanus toxoids (dT) may prolong the immunity against pertussis infection. GlaxoSmithKline (GSK) Biologicals has developed a dTpa vaccine for booster vaccination of children, adolescents and adults against diphtheria, tetanus and pertussis diseases, known as *Boostrix*. *Boostrix* was first licensed for use in Germany in 1999 and is indicated for booster vaccination in individuals aged four years and older [Mertsola, 2010]. *Boostrix* vaccine contains 0.5 mg Al (as aluminium

phosphate and aluminium hydroxide) per 0.5 millilitre (ml) dose. *Boostrix* is currently not registered in Russia. This study will assess the immunogenicity, reactogenicity and safety of *Boostrix* in healthy Russian subjects aged four years and older. The data obtained from this study will be used to support the registration of *Boostrix* in Russia for individuals aged four years and older.

### 1.2.2. Rationale for the study design

The study is designed as an open-label, single group trial in which all the study subjects will receive a single dose of *Boostrix* vaccine. An equal number of subjects are expected to be recruited in the following age categories: 4-9 years (children), 10-17 years (adolescents), 18-64 years (adults) and ≥65 years (elderly population).

Pertussis outbreaks have occurred in a number of European and non-European countries. This resurgence is observed across the age range with a notable increase in cases now being detected in adolescents and older age groups. It is also now recognized that immunity following either natural pertussis infection or vaccination is not long lived, and the acellular pertussis vaccines that have been widely used since the 1990s may be more prone to such waning. Consequently, adults and adolescents with pertussis are a potential source of infection for infants too young to have been fully vaccinated. Many countries recommend 'cocoon ' strategy, i.e. vaccination of family members and close contact of newborn (i.e. grandparents usually above 65 years old), in order to protect infants from acquiring pertussis. The ≥65 years (elderly population) have therefore been included in the study.

## 1.3. Benefit: Risk Assessment

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

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 (*Boostrix*)** | | |
| 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. |
| Syncope | As outlined in the Reference Safety Information (RSI), syncope (fainting) can occur following or even before any vaccination especially in adolescents as a psychogenic response to the needle injection. | It is important that procedures are in place to avoid injury from fainting. 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. |
| **Study Procedure** | | |
| Risk from blood sampling. | Blood sampling associated risk of discomfort, syncope, infection at the site after or during venipuncture | Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health. |

### 1.3.2. Benefit Assessment

Diphtheria, tetanus and pertussis are common causes of diseases in children worldwide, with significant morbidity and mortality. A dramatic decline in the incidence of diphtheria, tetanus, and pertussis has been evidenced in countries in which infants are routinely immunised against these diseases. Clinical trial and post-marketing data demonstrate the substantial benefit of *Boostrix* vaccination worldwide. By receiving the *Boostrix* vaccine, the subjects may be protected against diphtheria, tetanus and pertussis diseases.

### 1.3.3. Overall Benefit: Risk Conclusion

Based on the assessment of the extensive safety database following *Boostrix* vaccination and taking into account the measures taken to minimise risk to subjects participating in this study, the potential or identified risks identified in association with *Boostrix* vaccination, are justified by the potential benefits (prevention) that may be afforded to subject(s) receiving *Boostrix* vaccination.

# 2. OBJECTIVES

## 2.1. Primary objective

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

Refer to Section 10.1 for the definition of the primary endpoint.

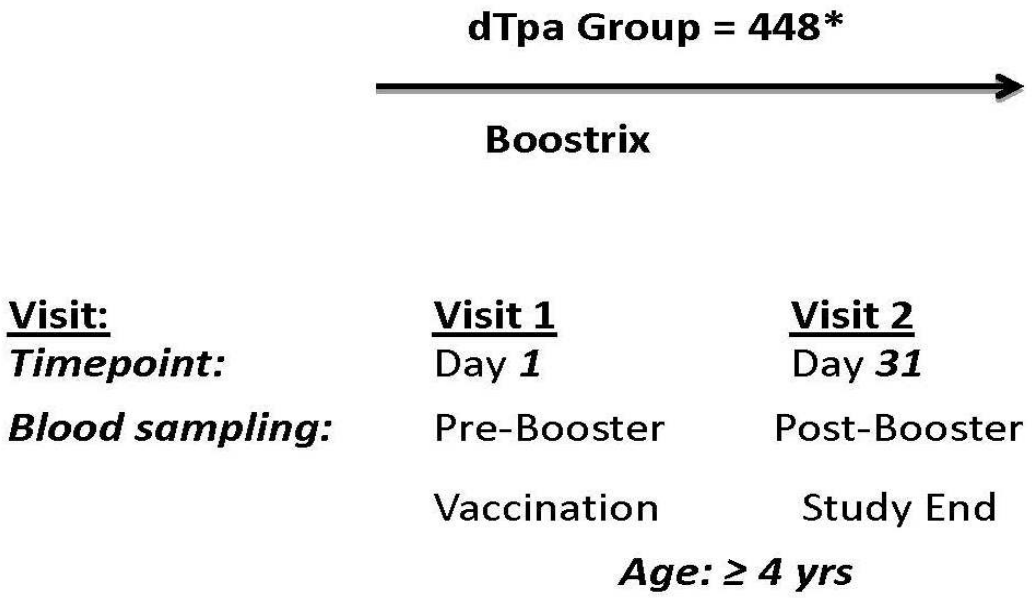
## 2.2. Secondary objectives

- To assess the immune response in terms of booster response* to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.
- To assess the immune response in terms of antibody concentrations to diphtheria, tetanus, PT, FHA, and PRN antigens, one month after vaccination.
- To assess the reactogenicity and safety of *Boostrix* in terms of solicited symptoms (local and general), unsolicited adverse events (AEs) and serious adverse events (SAEs).

*Refer to Section 10.5 for the definition of booster response.

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

# 3. STUDY DESIGN OVERVIEW




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

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

- Experimental design: Phase III, open-label, non-randomised, multi-centric, single-country study with a single group.
- Duration of the study:
  - Epoch 001: Primary Epoch starting at Visit 1 (Day 1) and ending at Visit 2 (Day 31)
- Primary Completion Date (PCD): Visit 2 (Day 31)

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit 2.

Refer to glossary of terms for the definition of EoS.

- Study groups: The study group and epoch foreseen in this study is presented in Table 1.

**Table 1 Study group and epoch foreseen in the study**

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

**Table 2 Study group and treatment foreseen in the study**

| Treatment name | Vaccine/Product name | Study Group |
|---|---|---|
| | | dTpa Group |
| *Boostrix* | dTpa | x |

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

**Table 3 Blinding of study epoch**

| Study Epoch | Blinding |
|---|---|
| Epoch 001 | open |

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

# 4. STUDY COHORT

## 4.1. Number of subjects/centres

Approximately 448 subjects are expected to be enrolled in this study. An equal number of subjects (approximately 112) are expected to be recruited in each of the following age categories: 4-9 years (children), 10-17 years (adolescents), 18-64 years (adults) and ≥65 years (elderly population) in order to evaluate data. Refer to Section 10.1 for a detailed description of criteria used for the estimation of sample size.

Overview of the recruitment plan:

- The study will take place at multiple centres in Russia.
- The recruitment of subjects into the study will be tracked using GSK Biologicals' central randomisation system on Internet (SBIR).
- Recruitment will be monitored by the site monitor.

## 4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study 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 or subjects' parent(s)/adoptive parent(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).
- A male or female four years of age and older.
- Written informed consent obtained from the subject/from the parent(s)/adoptive parent(s) of the subject prior to performing any study specific procedure.
- Written informed assent obtained from subjects aged 14 years to <18 years.
- Healthy subjects as established by medical history and physical examination before entering into the study.
- Children 4-7 years of age with documented previous diphtheria, tetanus and pertussis vaccination (primary series and first booster) as per local recommendation prior to study enrolment, but should have not received any further diphtheria-tetanus containing booster planned at 6-7 years of age as per local recommendations or any other diphtheria, tetanus and pertussis containing vaccine.

  OR

- Subjects eight years of age and older who can report previous diphtheria, tetanus ***with or without*** pertussis vaccination – documented or to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge – and did not receive an additional diphtheria, tetanus ***with*** or ***without*** pertussis vaccination within five years prior to enrolment in the study will be enrolled. (**Amended 31 October 2017**)
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

  Please refer to the glossary of terms for the definition of menarche and menopause.
- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - has practiced adequate contraception within 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination, and
  - has agreed to continue adequate contraception during the entire treatment period and for one month after completion of the vaccination.

Please refer to the glossary of terms for the definition of adequate contraception.

## 4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study 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.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the dose of study vaccine, or planned use during the study period.
- History of previous or intercurrent diphtheria, tetanus or pertussis diseases since birth in subjects four to seven years of age.
- History of previous or intercurrent diphtheria, tetanus or pertussis diseases within five years prior to enrolment in subjects aged eight years and above.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the vaccine dose. For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects, ≥18 years of age) or ≥0.5 mg/kg/day (for paediatric subjects, aged 4-17 years), 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).
- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after the dose of vaccine with the exception of inactivated influenza vaccine which can be given at any time during the study conduct as per the Summary of Product Characteristics (SmPC) and according to the local governmental recommendations.
- 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).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, 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.
- Hypersensitivity to latex.
- History of encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) after administration of a previous dose of pertussis vaccine that could not be attributed to another identifiable cause, progressive neurologic disorder,

uncontrolled epilepsy or progressive encephalopathy: pertussis vaccine should not be administered to individuals with these conditions until a treatment regimen has been established and the condition has stabilized.

- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥38.0°C. The preferred location for measuring temperature in this study will be the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Acute or chronic, clinically significant uncontrolled pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination and/or laboratory screening tests.
- Administration of immunoglobulins and/or any blood products within the three months preceding the dose of study vaccine or planned administration during the study period.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions during the study conduct.
- Any medical condition that, in the opinion of the investigator, might interfere with the evaluations required by the study.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.

# 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 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/subject's parent(s)/adoptive parent (s) informed consent and subject informed assent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

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

Freely given and written or witnessed informed consent must be obtained from each subject and/or each subject's parent(s)/adoptive parent(s) and subject informed assent, 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.

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, those subjects who can only be enrolled in the study with the consent of the subject's ***parent(s)/adoptive parent(s)*** (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent form (IAF). It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by his/her legal representative. It should be assessed whether an assent is required depending of the age of the study population and the local requirements **(Amended 31 October 2017).**

GSK Biologicals strongly recommends that if the subject reaches the age of consent during the study they will be asked to provide consent at the next study visit (if applicable). This procedure should be applied according to local laws and regulations.

The investigator has the final responsibility for the final presentation of the ICF and IAF, respecting the mandatory requirements of local regulations. The ICF and IAF 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

### 5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.

### 5.2.2. Randomisation of treatment

#### 5.2.2.1. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

##### *5.2.2.1.1. Study group and treatment number allocation*

The enrolment will be performed to ensure equal distribution of the population across the four age strata [4-9 years (children), 10-17 years (adolescents), 18-64 (adults) years and ≥65 years (elderly population)]. Therefore, the expected distribution of subjects is as shown in Table 4.

**Table 4 Number of subjects required for enrolment**

| Age Stratum | Vaccine | N |
|---|---|---|
| 4-9 years | *Boostrix* | 112 |
| 10-17 years | *Boostrix* | 112 |
| 18-64 years | *Boostrix* | 112 |
| ≥65 years | *Boostrix* | 112 |

N = approximate number of subjects to be enrolled

Allocation of a treatment number to the subject at the investigator site will be performed using a randomisation system on internet (SBIR).

After obtaining the signed and dated ICF and IAF (if applicable) from the subject and having checked the eligibility of the subject, the study staff in charge of the vaccine administration will access SBIR. Upon providing the age [4-9 years (children), 10-17 years (adolescents), 18-64 years (adults) and ≥65 years (elderly population)] and the subject identification number, the randomisation system will provide the treatment number to be used for the dose.

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

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

## 5.3. Method of blinding

This is an open-label study as all the subjects will receive a booster dose of *Boostrix*.

## 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.

## 5.5. Outline of study procedures

The list of study procedures is presented in Table 5.

## Table 5 List of study procedures

| Epoch | Epoch 001 | |
|---|---|---|
| **Type of contact** | **Visit 1** | **Visit 2** |
| **Timepoints** | **Day 1** | **Day 31** |
| **Sampling timepoints** | **Pre-Bst** | **Post-Bst** |
| Informed consent | ● | |
| Informed assent | O | |
| Check if minor subject reaches legal age and needs to provide consent | | O |
| Check inclusion/exclusion criteria | ● | |
| Collect demographic data | ● | |
| Medical history and vaccination history | ● | |
| Physical examination# | ● | O |
| Urine pregnancy test [1] | ● | |
| Check contraindications and warnings and precautions for vaccination | O | |
| Pre-vaccination body temperature | ● | |
| **Laboratory assays** | | |
| Blood sampling for antibody determination (approx. 5 ml) | ● | ● |
| **Vaccine** | | |
| Treatment number allocation | O | |
| Recording of administered treatment number | ● | |
| Vaccine administration | ● | |
| Observation of subject for minimum 30 minutes following vaccination | O | |
| **Safety assessments** | | |
| Record any concomitant medication/vaccination | ● | ● |
| Record any intercurrent medical conditions | ● | ● |
| Distribution of diary cards | O | |
| Recording of solicited adverse events within 4 days (Day 1–4) post-vaccination by subjects/subjects' parent(s)/adoptive parent(s) | ● | |
| Record large injection site reactions[2] | ● | |
| Recording of non-serious adverse events within 31 days (Day 1-31) post-vaccination, by subjects/subjects' parent(s)/adoptive parent(s) | ● | ● |
| Return of dairy cards | | O |
| Diary card transcription by investigator | | ● |
| Recording of serious adverse events (SAEs) | ● | ● |
| Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine | ● | ● |
| Recording of pregnancies[1] | ● | ● |
| Recording of AEs leading to withdrawal from the study | ● | ● |
| 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
# Physical examination after the vaccination visit, will be performed only if the subject/subject's parent(s)/adoptive parent(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.
Pre-Bst: Before the administration of study vaccine; Post-Bst: one month after the administration of study vaccine.
1 Applicable to women of child-bearing potential.
2 Refer to the table notes under Table 12 for a detailed explanation on the reporting of large injection site reactions by the subject's/subjects' parent(s)/adoptive parent (s).

The interval between study visits is presented in Table 6.

**Table 6 Intervals between study visits**

| Interval | Optimal length of interval[1] | Allowed interval[2] |
|---|---|---|
| Visit 1→Visit 2 | 30 days | 21 days-48 days |

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] An interval of 21-48 days between Visit 1 and Visit 2 will be considered for the Per Protocol (PP) cohort of immunogenicity. Refer to Section 10.4 for the definition of the cohorts for analysis. If subjects return for the visits prior to 30 days, they should take the diary card home and continue to record unsolicited safety information until 30 days post-vaccination and mail/send it upon completion. Investigators should transcribe any data already collected on the cards prior to sending it back home with the subjects. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

## 5.6. Detailed description of study procedures

### 5.6.1. Informed consent

The signed/witnessed informed consent of the subject/subject's parent(s)/adoptive parent (s) must be obtained before study participation. The signed informed assent of the subject below the age of consent (i.e. minor) should be obtained in addition to the signed informed consent by his/her parent(s)/adoptive parent (s) according to local rules and regulations. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

### 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 at vaccination visit in months and years, gender and geographical ancestry in the subject's eCRF.

### 5.6.4. Medical history and vaccination history (Amended 31 October 2017)

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

Review the subject's* childhood diphtheria, tetanus***, with or without*** pertussis**,** vaccinations to collect information on the vaccine name, route of administration, dose number and date of administration. This information should be recorded in the eCRF.

*For subjects eight years and older, with no documented previous diphtheria, tetanus**, with or without*** pertussis**,** vaccinations, details are to be recorded to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge.

### 5.6.5. Physical examination

Perform a physical examination of the subject, including recording of height and weight (for calculation of BMI), assessment of body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest. Collected information needs to be recorded in the eCRF.

Physical examination after the vaccination visit, will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

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

### 5.6.6. Urine pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

### 5.6.7. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of the 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 the study vaccine administration. The preferred route for recording temperature in this study will be axillary. If the subject has fever [Fever is defined as temperature ≥38.0°C. The preferred location for measuring temperature in this study will be the axilla] on the day of vaccination, the vaccination visit will be rescheduled.

### 5.6.9. Sampling

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

#### 5.6.9.1. Blood sampling for antibody determination

Blood samples will be taken at Visit 1 and Visit 2 as specified in Section 5.5, List of Study Procedures.

- A volume of approximately 5 ml of whole blood (to provide approximately 1. 7 ml of serum) should be drawn from all subjects at the pre-booster and post-booster timepoint (Visit 1 and Visit 2). After centrifugation, serum samples should be kept at –20°C or below until shipment.

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

### 5.6.10. Study Vaccine administration

- After completing all prerequisite procedures prior to vaccination, the study vaccine will be administered intramuscularly in the deltoid muscle of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled.
- 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.

### 5.6.11. 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.

### 5.6.12. Distribution of diary cards and recording of AEs, SAEs and pregnancies

- Refer to Section 8.3 for procedures for the investigator or delegate to record AEs, SAEs, and pregnancies. Refer to Section 8.4 for guidelines and how to report SAE, and pregnancy reports to GSK Biologicals.
- The subjects/subjects' parent(s)/adoptive parent (s) will be instructed to contact the investigator or delegate immediately should they/the subjects manifest any signs or symptoms they perceive as serious.
- At Visit 1, diary cards will be provided to the subject/subject's parent(s)/adoptive parent(s). The subject/subject's parent(s)/adoptive parent(s) will record body (preferably axillary) temperature and any solicited local/general AEs (i.e. on the day

of vaccination and during the next three days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days) occurring after vaccination. The subject/subject's parent(s)/adoptive parent(s) will be instructed to return the completed diary card to the investigator or delegate at the next study visit.

  - Note: Diary cards can be filled in by a minor subject under the supervision of the subject's parent(s)/adoptive parent(s) provided that the minor has the competency to assess and report the information to be provided in the diary card. The ultimate accountability for the completion of the diary cards remains with the subject's parent(s)/adoptive parent(s). The investigator or delegate should discuss this accountability with the subject's parent(s)/adoptive parent(s).

- Collect and verify completed diary cards during discussion with the subject/subject's parent(s)/adoptive parent(s) on Visit 2.

  - Note: If the diary card has been filled in by a minor subject, the investigator or delegate should verify the reported information during a discussion with the minor subject preferably in the presence of his/her parent(s)/adoptive parent(s).

- After vaccination, if the subjects or the subject's parents/adoptive parents observe any large injection site reaction (for subjects <6 years of age defined as a swelling with a diameter of >50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm, noticeable diffuse swelling or noticeable increase in limb circumference) during the 4-day follow-up (Day 1-4) period, they will be asked to contact study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator or delegate will record detailed information describing the AE on a specific large injection site reaction screen in the eCRF.

### 5.6.13. Return of diary card and diary card transcription

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

### 5.6.14. Recording of AEs, SAEs and pregnancies

- Refer to Section 8.3 for procedures for the investigator or delegate to record AEs, SAEs, pregnancies. Refer to Section 8.4 for guidelines and how to report SAE and pregnancy reports to GSK Biologicals.
- The subject/subjects' parent(s)/adoptive parent(s) will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.

### 5.6.15. Study conclusion

The investigator will:

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

## 5.7. Biological sample handling and analysis

Please refer to the SPM for details on Biospecimen Management (handling, storage and shipment).

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 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 Russia and will only be performed once an IEC or IRB 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/subject's parent(s)/adoptive parent(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 per protocol (PP) 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 required for this study have been presented in Table 7.

**Table 7 Biological samples**

| Sample type | Quantity | Unit | Timepoint |
|---|---|---|---|
| Blood | Approximately 5 | ml | Pre-Bst[1] and Post-Bst[2] |

[1] Pre-Bst: Before the administration of study vaccine.
[2] Post-Bst: one month after the administration of study vaccine.

### 5.7.3. Laboratory assays

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

All serology will be determined in GSK Biologicals' laboratories or in a laboratory designated by GSK using standardized and validated procedures with adequate controls.

Refer to Table 8 for the assays used in antibody determination.

**Table 8 Humoral Immunity (Antibody determination)**

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

ELI: ELISA
NEU: Neutralisation assay
NA: Not Applicable
IU/ml: International Units per millilitre
†***ELISA's*** for diphtheria, tetanus and pertussis were re-developed and re-validated as per most recent CBER recommendations (Guidance for Industry "Bioanalytical Method Validation" from September 2013). The new assay cut-off's that apply are listed in the table. ***The neutralisation assay for Diphtheria is still under re-development and the assay cut-off might be subject to change during the course of the study. In this case, it will be documented in the clinical study report.*** **(Amended 31 October 2017)**
*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium and Wavre, Belgium.
**Test on Vero-cells will be performed on pre- and post-vaccination samples with concentrations <0.1 IU/ml by ELISA.

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 9.

**Table 9 Immunological read-outs**

| Blood sampling timepoint | | No. of subjects | Component | Components priority rank |
|---|---|---|---|---|
| Type of contact and timepoint | Sampling timepoint | | | |
| Visit 1 (Day 1) | Pre-Bst[1] | All | PT, FHA, PRN,<br>Diphtheria (ELISA), Tetanus<br>Diphtheria (Vero-cell*) | 1<br>2<br>3 |
| Visit 2 (Day 31) | Post-Bst[1] | All | PT, FHA, PRN,<br>Diphtheria (ELISA), Tetanus<br>Diphtheria (Vero-cell*) | 1<br>2<br>3 |

[1] Pre-Bst: Before the administration of study vaccine; Post-Bst: one month after the administration of study vaccine.
* Test on Vero-cells will be performed on pre- and post-vaccination samples with concentrations <0.1 IU/ml by ELISA.

### 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 newly validated assay cut-off for anti-diphtheria is currently set at 0.057 IU/ml and for anti-tetanus at 0.043 IU/ml. For both serology a threshold of 0.1 IU/ml provides a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983].
- The cut-off of the Vero-cell neutralisation assay (performed for pre- and post-vaccination serum samples when ELISA anti-diphtheria antibody concentrations are <0.1 IU/ml) is 0.004 IU/ml. Antibody concentrations ≥0.01 IU/ml are considered as protective [***WHO, 1994***]. ***Both the*** ELISA test ***(antibody concentrations ≥0.1 IU/ml) and Vero-cell test (antibody concentration ≥0.01 IU/ml)*** will define the seroprotection status for the primary endpoint. (**Amended 31 October 2017**)
- No serological correlate of protection is defined for the immune response to pertussis antigens. Antibodies against the pertussis components PT, FHA and PRN will be measured by ELISA technique. The newly validated assay cut-off for anti-PT is 2.693 IU/ml, for anti-FHA is 2.046 IU/ml and for anti-PRN is 2.187 IU/ml. Subjects with antibody concentration below this cut-off will be considered seronegative.

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/subjects' parent(s)/adoptive parent(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.

Non-responders are defined as:

- Antibody concentrations <0.01 IU/ml post-booster for diphtheria antigen by Vero-cell neutralisation assay and,
- Antibody concentrations <0.1 IU/ml post-booster for tetanus antigen by ELISA assay.

# 6. STUDY VACCINE AND ADMINISTRATION

## 6.1. Description of study vaccine

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

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

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

Table 10 presents the details of the study vaccine and administration.

**Table 10 Study vaccine**

| Treatment name | Vaccine name | Formulation | Presentation | Volume to be administered | Number of doses |
|---|---|---|---|---|---|
| *Boostrix* | dTpa | DT>=2IU; TT>=20IU; PT=8µg; FHA=8µg; PRN=2.5µg; Aluminium=500µg Al3+ | Pre-filled syringes, Homogeneous turbid white suspension | 0.5 ml | 1 |

DT: Diphtheria toxoid, TT: Tetanus toxoid, PT: Pertussis toxoid, FHA: Filamentous haemagglutinin, PRN: Pertactin, Aluminium as $Al(OH)_5$.

## 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 authorised study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study 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) or above -15.0°C (for -20°C/-4°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form (ATEAM). 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 ATEAM, 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 vaccine

The vaccine will be administered as detailed in Table 11.

The vaccine will be administered as an IM injection into the deltoid muscle of the non-dominant arm, i.e. in the left arm if the subject is right-handed or in the right arm if the subject is left-handed. In case it is not possible for a valid reason to inject in the non-dominant arm, an injection in the dominant arm may be performed. *Boostrix* should in no circumstances be administered intravascularly.

In order to ensure proper IM injection of the vaccine, a needle of 1-1½ inch length, 25 gauge will be used [Zuckerman, 2000]. Needle of 21-25 gauge can be used depending on the age of the subjects.

**Table 11 Dosage and administration**

| Type of contact and timepoint | Volume to be administered | Study Group | Treatment name | Route | Site | Side |
|---|---|---|---|---|---|---|
| Visit 1 (Day 1) | 0.5 ml | dTpa Group | *Boostrix* | IM | Deltoid | Non-dominant |

IM: Intramuscular

## 6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 5% additional vaccine doses will be supplied to replace those that are unusable.

## 6.5. Contraindications to vaccination

Since this is a single dose study, contraindications to vaccination are included in the exclusion criteria. Refer to Section 4.3.

The following events constitute contraindications to administration of Boostrix at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 6.7.1), or the subject may be withdrawn at the discretion of the investigator (see Section 6.7.2).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C. The preferred location for measuring temperature in this study will be the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered the study vaccine.

## 6.6. Warnings and precautions

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after vaccination.

Boostrix vaccination should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular (IM) administration to these subjects.

Boostrix vaccination should under no circumstances be administered intravenously.

## 6.7. Concomitant medications/products and concomitant vaccinations

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

### 6.7.1. Recording of concomitant medications/products and concomitant vaccinations

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

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period starting from the administration of study vaccine (Day 1) and ending at Visit 2 (Day 31).

- Any concomitant vaccination administered in the period starting from the administration of study vaccine (Day 1) and ending at the last study visit [Visit 2 (Day 31)].
- 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 ≥38.0°C. The preferred location for measuring temperature in this study will be the axilla.
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as PP 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 in eCRF.

### 6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per protocol 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 PP analysis. See Section 10.4 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting from the dose of study vaccine (Day 1) and ending 31 days after the dose of vaccine administration, with the exception of influenza vaccine which is allowed throughout the study period.
- In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics (SmPC) and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period.

### 6.8. Intercurrent medical conditions that may lead to elimination of a subject from per protocol analyses

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

Subjects may be eliminated from the PP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status.

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

### 8.1. Safety definitions

#### 8.1.1. Definition of an adverse event

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

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

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

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

Examples of an AE DO NOT include:

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

### 8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

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

c. Requires hospitalisation or prolongation of existing hospitalisation,

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

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

d. Results in disability/incapacity, OR

   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.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

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 12 Solicited local adverse events**

| All age groups |
|---|
| Pain at injection site |
| Redness at injection site |
| Swelling at injection site |

Note: If the subjects or the subject's parent(s)/adoptive parent(s) observe any large injection site reaction (for subjects <6 years of age defined as a swelling with a diameter of > 50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm, noticeable diffuse swelling or noticeable increase in limb circumference) during the 4-day (Day 1–4) follow-up period after vaccination, they will be asked to contact the study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator or delegate will record detailed information describing the AE on a specific large injection site reaction sheet in the eCRF.

### 8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

**Table 13 Solicited general adverse events**

| Toddler/Child (<6 years) |
|---|
| Drowsiness |
| Fever |
| Irritability/Fussiness |
| Loss of appetite |

| Adult/Child (≥6 years) |
|---|
| Fatigue |
| Fever |
| Gastrointestinal symptoms † |
| Headache |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

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.

Subjects/parent(s)/adoptive parent(s) will be instructed to measure and record the body temperature by axillary route in the evening. Should additional temperature measurements be performed at other times of day, subjects/parent(s)/adoptive parent(s) will be instructed to record the highest temperature in the diary card.

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

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

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. Events or outcomes not qualifying as adverse events or serious adverse events

### 8.2.1. Pregnancy

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.4.1 and 8.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation)

  Note: The 22 weeks' cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first seven days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy and considered by the investigator to be reasonably related to the study vaccine will be reported to GSK Biologicals as described in Section 8.4.3. While the investigator or delegate is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

## 8.3. Detecting and recording adverse events, serious adverse events and pregnancies

### 8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs starting within 30 days following administration of the dose of study vaccine (Day 1-31) must be recorded onto the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the receipt of study vaccine and will end 30 days following administration of the dose of study vaccine for each subject. See Section 8.4 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 receipt of study vaccine.

SAEs that are related to the study vaccine will be collected and recorded from the time of the 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 subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine and will end 30 days following administration of the dose of study vaccine. All pregnancies recorded during this period will be followed up as detailed in sections 8.2.1, 8.4 and 8.5.2.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 14.

**Table 14 Reporting periods for collecting safety information**

| Event Timepoint | Pre-Bst (consent obtained) | Vaccination (Day 1) | Post Bst (Day 1-4) | Post Bst (Day1-31) |
|---|---|---|---|---|
| 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/vaccination | | | | |
| Pregnancies* | | | | |

Pre-Bst: Before the administration of study vaccine; Post-Bst: After the administration of study vaccine.
*This refers to collecting information on pregnancy as an event and not as an outcome, which will be collected after the end of the study.

### 8.3.2. 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 14. Investigator(s) or delegate(s) is/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.

### 8.3.3. Evaluation of adverse events and serious adverse events

#### 8.3.3.1. Active questioning to detect adverse events and serious adverse events

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

'*Have you felt different in any way since receiving the vaccine(s)/product(s) or since the previous visit?*'

'*Has your child acted differently or felt different in any way since receiving the vaccine(s)/product(s) 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 or delegate will then record all relevant information regarding an AE/SAE in the eCRF. The investigator or delegate 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.

#### 8.3.3.2. Assessment of adverse events

##### *8.3.3.2.1. Assessment of intensity*

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

**Table 15 Intensity scales for solicited symptoms in children less than six years of age**

| Toddler/Child (<6 years) | | |
|---|---|---|
| **Adverse Event** | **Intensity grade** | **Parameter** |
| Pain at injection site | 0 | None |
| | 1 | Mild: Minor reaction to touch |
| | 2 | Moderate: Cries/protests on touch |
| | 3 | Severe: Cries when limb is moved/spontaneously painful |
| Redness at injection site | | Record greatest surface diameter in mm |
| Swelling at injection site | | Record greatest surface diameter in mm |
| Fever* | | Record temperature in °C |
| Irritability/Fussiness | 0 | Behaviour as usual |
| | 1 | Mild: Crying more than usual/no effect on normal activity |
| | 2 | Moderate: Crying more than usual/interferes with normal activity |
| | 3 | Severe: Crying that cannot be comforted/prevents normal activity |
| Drowsiness | 0 | Behaviour as usual |
| | 1 | Mild: Drowsiness easily tolerated |
| | 2 | Moderate: Drowsiness that interferes with normal activity |
| | 3 | Severe: Drowsiness that prevents normal activity |
| Loss of appetite | 0 | Appetite as usual |
| | 1 | Mild: Eating less than usual/no effect on normal activity |
| | 2 | Moderate: Eating less than usual/interferes with normal activity |
| | 3 | Severe: Not eating at all |

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

**Table 16 Intensity scales for solicited symptoms in adults and children of six years of age or more**

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

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

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

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

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

| | | |
|---|---|---|
| 0 | : | Absent |
| 1 | : | ≤20 mm |
| 2 | : | >20 mm and ≤50 mm |
| 3 | : | >50 mm |

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

| | | |
|---|---|---|
| 0 | = | <38°C |
| 1 | = | ≥38.0°C to ≤39.0°C |
| 2 | = | >39.0°C to ≤40.0°C |
| 3 | = | >40.0°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.<br>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)/adoptive parent(s) to seek medical advice. In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy. |
| 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. | | |

#### *8.3.3.2.2. Assessment of causality*

The investigator is obligated to assess the relationship between study vaccine and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the AE to be related to all products.

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 study vaccine will be considered and investigated. The investigator will also consult the IB and/or SmPC for marketed products 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 vaccine contributed to the AE. |
| NO | : | There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine 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).

#### 8.3.3.3. 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).

## 8.4. Reporting of serious adverse events, pregnancies, and other events

### 8.4.1. Prompt reporting of serious adverse events and pregnancies to GSK Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pregnancy.

**Table 17 Timeframes for submitting serious adverse event and pregnancy reports to GSK Biologicals**

| Type of Event | Initial Reports | | Follow-up of Relevant Information on a Previous Report | |
|---|---|---|---|---|
| | Timeframe | Documents | Timeframe | Documents |
| SAEs | 24 hours*‡ | electronic Expedited Adverse Events Report | 24 hours* | electronic Expedited Adverse Events Report |
| Pregnancies | 2 weeks* | electronic pregnancy report | 2 weeks* | electronic pregnancy 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.

### 8.4.2. Contact information for reporting serious adverse events, pregnancies and pIMDs

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

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

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

#### 8.4.3.1. 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.

### 8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

### 8.4.5. Updating of SAE and pregnancy information after removal of write access to the subject's eCRF

When additional SAE and pregnancy 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 17.

### 8.4.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. 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 study vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

## 8.5. Follow-up of adverse events, serious adverse events, and pregnancies

### 8.5.1. Follow-up of adverse events and serious adverse events

#### 8.5.1.1. 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 17).

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 vaccination.

#### 8.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

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

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

### 8.5.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

## 8.6. 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 a SAE should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.7).

## 8.7. Subject card

Study subjects/subjects' parent(s)/adoptive parent(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/subject's parent(s)/adoptive parent(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/subjects' parent(s)/adoptive parent(s) must be instructed to keep subject cards in their possession at all times during the study duration.

# 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 or delegate will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, by the subject's parent(s)/adoptive parent(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited 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 he/she/the subject's parent(s)/adoptive parent(s) has withdrawn consent, the investigator or delegate will document the reason for withdrawal of consent, if specified by the subject/subject's parent(s)/adoptive parent(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 8.5.1.2).

# 10. STATISTICAL METHODS

## 10.1. Primary endpoint

- Immunogenicity with respect to components of the study vaccine.
  - Anti-diphtheria* and anti-tetanus seroprotection status, one month after vaccination.
  - Anti-PT, anti-FHA and anti-PRN seropositivity status, one month after vaccination.

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

## 10.2. Secondary endpoints

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

- Serious adverse events.
  - Occurrence of SAEs from the vaccination up to study end.

*Refer to Section 10.5 for the definition of booster response.

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

## 10.3. Determination of sample size

The primary objective of the study is to assess the immunological response to the study vaccine in terms of seroprotection status for diphtheria, tetanus and in terms of seropositivity for the pertussis antigens, one month after vaccination.

According to Russian regulations, for the purpose of product registration, the minimum sample size required is 100 subjects in each age group. Therefore, the total number of evaluable subjects is 400 [100 subjects in each age group, 4-9 years (children), 10--17 years (adolescents), 18-64 years (adults) and ≥65 years (elderly population)]. Assuming a drop-out rate of 10%, to compensate for subject attrition due to early withdrawal, a total of 448 subjects (112 in each age group) will be enrolled in to the study in order to obtain the desired number of evaluable subjects for analysis.

Table 18, Table 19, Table 20 present the exact two-sided 95% confidence interval (CI) for a sample size of 400 subjects, according to the value observed for the seroprotection status for diphtheria and tetanus, seropositivity for the pertussis antigens and booster response to all antigens.

In addition, Table 21 presents the exact two-sided 95% CI for a sample size of 100 subjects (per age category), according to the value observed for the seroprotection status for diphtheria and tetanus, seropositivity for the pertussis antigens and booster response to all antigens.

**Table 18 Exact two-sided 95% CI for a sample size of 400 subjects according to the value observed for seroprotection status for diphtheria and tetanus**

| Observed rate expressed as a percentage (number of subjects reporting seroprotection for diphtheria and tetanus antigens) | Exact two-sided 95% CI for this observed rate for a sample size of 400 subjects | |
|---|---|---|
| | Lower Limit | Upper Limit |
| 90(360) | 86.6 | 92.8 |
| 91.1(364) | 87.8 | 93.6 |
| 95(380) | 92.4 | 96.9 |
| 96.2(385) | 93.9 | 97.9 |
| 99.5(398) | 98.2 | 99.9 |
| 100(400) | 99.1 | 100 |

Reference data: Please refer Table 22.

**Table 19 Exact two-sided 95% CI for a sample size of 400 subjects according to the seropositivity for the pertussis antigens**

| Observed rate expressed as a percentage (number of subjects reporting seropositivity for the pertussis antigens) | Exact two-sided 95% CI for this observed rate for a sample size of 400 subjects | |
|---|---|---|
| | Lower Limit | Upper Limit |
| 90(360) | 86.6 | 92.8 |
| 95(380) | 92.4 | 96.9 |
| 98.6(394) | 96.8 | 99.4 |
| 99.1(396) | 97.5 | 99.7 |
| 99.5(398) | 98.2 | 99.9 |
| 100(400) | 99.1 | 100 |

Reference data: Please refer Table 22.

**Table 20 Exact two-sided 95% CI for a sample size of 400 subjects according to the value observed for the primary endpoints and the Booster response to all antigens**

| Observed rate expressed as a percentage (number of subjects reporting Booster response to all antigens) | Exact two-sided 95% CI for this observed rate for a sample size of 400 subjects | |
|---|---|---|
| | Lower Limit | Upper Limit |
| 75(300) | 70.5 | 79.2 |
| 79(316) | 74.7 | 82.9 |
| 80(320) | 75.7 | 83.8 |
| 80.6(322) | 76.3 | 84.3 |
| 81.2(325) | 77.1 | 85 |
| 84.6(338) | 80.6 | 87.9 |
| 85(340) | 81.1 | 88.4 |
| 89.3(357) | 85.8 | 92.1 |
| 90(360) | 86.6 | 92.8 |
| 92.1(368) | 88.9 | 94.5 |
| 92.8(371) | 89.8 | 95.1 |
| 94.3(377) | 91.5 | 96.3 |
| 95(380) | 92.4 | 96.9 |
| 96.8(387) | 94.5 | 98.3 |
| 98.9(396) | 97.5 | 99.7 |
| 99.5(398) | 98.2 | 99.9 |
| 100(400) | 99.1 | 100 |

Reference data: Please refer Table 22.

**Table 21 Exact two-sided 95% CI for a sample size of 100 (per age category) subjects according to the value observed for the seroprotection status for diphtheria and tetanus, seropositivity for the pertussis antigens and booster response to all antigens.**

| Observed rate expressed as a percentage (number of subjects reporting Booster response to all antigens) | Exact two-sided 95% CI for this observed rate for a sample size of 100 subjects | |
|---|---|---|
| | Lower Limit | Upper Limit |
| 75(75) | 65.3 | 83.1 |
| 79(79) | 69.7 | 86.5 |
| 80(80) | 70.8 | 83.8 |
| 81(81) | 71.9 | 88.2 |
| 84(84) | 75.3 | 90.6 |
| 85(85) | 76.5 | 91.4 |
| 89(89) | 81.2 | 94.4 |
| 90(90) | 82.4 | 95.1 |
| 92(92) | 84.8 | 96.5 |
| 94(94) | 87.4 | 97.8 |
| 95(95) | 88.7 | 98.4 |
| 96(96) | 90.1 | 98.9 |
| 98(98) | 93.0 | 99.8 |
| 99(99) | 94.6 | 100.0 |
| 100(100) | 96.4 | 100.0 |

Reference data: Please refer Table 22.

## Table 22 Reference values

| Study | Country | Population (Age in Years) | Vaccination History | N | D | T | PT | FHA | PRN | D VR | T VR | PT VR | FHA VR | PRN VR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DTPA (BOOSTRIX-045) 114778 | Mexico, Chile | 10-15 | 5/6X DTPa | 319 | 100 | 100 | 99.1 | 100 | 100 | 79 | 84.6 | 92.8 | 96.5 | 99.7 |
| DTPA (BOOSTRIX-002) 263855/002 | Australia | <40 | Heterogeneous | 214 | 96.2 | 100 | 99.5 | 100 | 100 | - | - | 96.2 | 100 | 99.1 |
| DTPA (BOOSTRIX-002) 263855/002 | Australia | ≥40 | Heterogeneous | 214 | 91.1 | 99.5 | 98.6 | 100 | 99.1 | - | - | 94.3 | 99.5 | 98.1 |
| DTPA (BOOSTRIX-004) 263855/004 | Finland | 10-14 | 4XDTPw | 447 | 100 | 100 | 98.4 | 100 | 100 | - | - | 92.1 | 96.8 | 98.9 |
| DTPA (BOOSTRIX-029) 263855/029 | Belgium | 10-18 | 4XDTPw | 218 | 99.5 | 100 | 100 | 100 | 100 | 80.6 | 81.2 | 89.3 | 97.7 | 98.1 |
| (APV-118 ) 208355/118 | Germany | 4-6 | 4XDTPa | 172 | 100 | 100 | 100 | 100 | 100 | - | - | 98.3 | 91.1 | 94.8 |
| DTPA (BOOSTRIX-034) 263855/034 | Belgium | ≥40 | Heterogeneous | 139 | 99.3 | 100 | 100 | 100 | 100 | 89.6 | 85.9 | 98.5 | 99.3 | 97.7 |
| DTPA (BOOSTRIX)-041 BST 029 (113055) | Belgium | 20-28 | 4XDTPw + booster DTPa | 60 | 100 | 100 | 100 | 100 | 100 | - | - | 94.1 | 96.0 | 67.3 |

N = number of subjects included in the PP cohort for immunogenicity

D and T: % of subjects with antibody concentration ≥0.1 IU/ml; PT, FHA and PRN: % of subjects with antibody concentration ≥5 EL.U/ml.

VR= Vaccine response:

Booster responses to the diphtheria and tetanus antigens, defined as:

For subjects with pre-vaccination concentration below seroprotection cut-off (<0.1 IU/ml): antibody concentrations at least ≥0.4 IU/ml one month after vaccination.

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

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

For initially seronegative subjects (pre-vaccination concentration below cut-off: <5 EL.U/ml): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥20 EL.U/ml)

For initially seropositive subjects with pre-vaccination concentration ≥5 EL.U/ml and <20 EL.U/ml: an increase in antibody concentrations of at least four times the pre-vaccination concentration.

For initially seropositive subjects with pre-vaccination concentration ≥20 EL.U/ml: an increase in antibody concentrations of at least two times the pre-vaccination concentration.

## 10.4. Cohorts for Analyses

Two cohorts are defined for the purpose of analysis:

- The Total vaccinated cohort (TVC).
- PP cohort for analysis of immunogenicity.

### 10.4.1. Total vaccinated cohort

- The TVC analysis will be performed per treatment actually administered. A safety analysis based on the TVC will include all subjects with the study vaccine administration documented.
- An immunogenicity analysis based on the TVC will include all subjects vaccinated and for whom data concerning at least one immunogenicity endpoint measure is available.

### 10.4.2. Per protocol cohort for analysis of immunogenicity

The PP cohort for immunogenicity will include all evaluable subjects:

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known and according to the protocol.
- Who have not received a vaccine not specified or forbidden in the protocol.
- Who meet all eligibility criteria.
- Who comply with the procedures and intervals defined in the protocol (Refer to Table 6).
- Who are within the maximum interval (the interval between Visit 1 and blood sampling at Visit 2, considered for inclusion of a subject will be 21–48 days) allowed as defined in the protocol.
- Who do not meet any of the criteria for elimination from an PP analysis (refer to Section 6.7.2).
- Who did not receive a product leading to exclusion from an PP analysis (refer to Section 6.7.2).
- Who did not present with a medical condition leading to exclusion from an PP analysis (refer to Section 6.8).
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component.

## 10.5. Derived and transformed data

- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- A seroprotected subject is a subject whose antibody concentration 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 ***for ELISA assay and ≥0.1 IU/ml for Vero-cell assay.*** **(Amended 31 October 2017)**
  - Anti-tetanus antibody concentrations ≥0.1 IU/ml.
- Other cut-offs to be considered:
  - Anti-diphtheria antibody concentrations ≥1.0 IU/ml.
  - Anti-tetanus antibody concentrations ≥1.0 IU/ml.
- Booster response to Diphtheria and Tetanus antigens is defined as:
  - for subjects with pre-vaccination antibody concentration <0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥0.4 IU/ml, one month after vaccination, and
  - for subjects with pre-vaccination antibody concentration ≥0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- Booster response to PT, FHA and PRN antigens is defined as:
  - for subjects with pre-vaccination antibody concentration below the assay cut-off, post-vaccination antibody concentration ≥ four times the assay cut-off,
  - for subjects with pre-vaccination antibody concentration between the assay cut-off and below four times the assay cut-off, post-vaccination antibody concentration ≥ four times the pre-vaccination antibody concentration, and
  - for subjects with pre-vaccination antibody concentration ≥ four times the assay cut-off, post-vaccination antibody concentration ≥ two times the pre-vaccination antibody concentration.
- The geometric mean concentration (GMC) calculations are performed by taking the anti-log of the mean of the $\log_{10}$ concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of 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.

**Reactogenicity and Safety:**

- For a given subject and the analysis of solicited symptoms during the 4-day post-vaccination follow-up period, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).
- For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication, respectively.
- For summaries reporting both solicited and unsolicited AEs, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication, respectively.

## 10.6. Analysis of demographics

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

- Frequency tables will be generated for categorical variable such as centre.
- Mean, median, standard deviation will be provided for continuous data such as age.
- The distribution of subjects based on age stratification will be tabulated (as seen in Table 23).

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

**Table 23 Age stratification**

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

## 10.7. Analysis of immunogenicity

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

For all subjects and each antigen:

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

In addition, the above analysis will also be done based on age stratification (Refer Table 23) as an exploratory analysis.

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

## 10.8. Analysis of safety

The analysis will be based on the TVC.

- The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 1-4) follow-up period after booster vaccination will be tabulated. The same calculations will be done for each individual solicited symptom rated as grade 3 in intensity and for each individual solicited symptom assessed as causally related to vaccination.
- Occurrence of fever during the 4-day follow-up period after vaccination will be reported per 0.5°C cumulative increments.
  - In addition, the above analysis will also be done for sub groups based on age stratification (Refer Table 23) as an exploratory analysis.
- The percentage of subjects with at least one local symptom (solicited or unsolicited), with at least one general symptom (solicited or unsolicited) and with any symptom (solicited or unsolicited) during the 4-day (Day 1-4) follow-up period after booster vaccination will be tabulated with exact 95% CI after booster vaccination. The same calculations will be done for symptoms (solicited or unsolicited) rated as grade 3 in intensity, for symptoms (solicited or unsolicited) leading to medical consultation and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.
- The percentage of subjects who started to receive at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day (Day 1-4) and 31-day (Day 1-31) follow-up period after vaccination will be tabulated with exact 95% CI.

- The verbatim reports of unsolicited AEs will be reviewed by a clinical research and development lead and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within the 31-day (Day 1-31) follow-up period after booster dose with its exact 95% CI will be tabulated by Preferred Term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.
- Any large injection site reaction (for subjects <6 years of age defined as a swelling with a diameter of >50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm, noticeable diffuse swelling or noticeable increase in limb circumference) onset during the 4-day (Day 1-4) follow-up period after vaccination will be described in detail.
- SAEs and withdrawal due to AEs and SAEs will be described in detail.

## 10.9. Interpretation of analyses

All analysis 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

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

### 10.10.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

# 11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, public disclosure requirements 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 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 other items, 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 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 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.

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. 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, otherwise, the minimum retention period will default to 25 years after completion of the study report.

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

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 PCD and to have secondary endpoint

disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

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.

## 11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non-GSK studies, to investigate further about the study product(s) and other product(s), and/or the disease/condition under investigation and related diseases and conditions.

# 12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

# 13. REFERENCES

Camargo ME, Silveira L, Furuta JA, et al. Immunoenzymatic assay of anti-diphtheric toxin antibodies in human serum. *J Clin Microbiol* 1984; 20(4): 772-4.

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf. Accessed on 02 February 2017.

Centers for Disease Control and Prevention (CDC)2015(a). Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition. April 2015. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pert.pdf. Accessed on 02 February 2017.

Centers for Disease Control and Prevention CDC 2015(b). http://www.cdc.gov/pertussis/fast-facts.html. Accessed on 02 February 2017.

de Greeff SC, Mooi FR, Westerhof A et al. Pertussis Disease Burden in the Household: How to Protect Young Infants. *Clin Infect Dis*. 2010; 50(10): 1339–1345.

***Efstratiou A. & Maple P.A.C., 1994. Diphtheria. Laboratory diagnosis of Diphtheria. The expended programme on immunization in the European region of WHO. WHO ICP/EPI 038 (C). World Health Organization, Geneva, Switzerland.*** **(Amended 31 October 2017)**

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (Doc. Ref. EMEA/CHMP/313666/2005) 'adopted at Community level in May 2006); http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf. Accessed on 02 February 2017.

Forsyth KD, Plotkin S, Tan T, et al. Strategies to Decrease Pertussis. *Pediatrics*. 2015;135(6): e1475 -82 (doi: 10.1542/peds.2014-3925).

Kowalzik F, Barbosa AP, Fernandes VR, et al. Prospective multinational study of pertussis infection in hospitalised infants and their household contacts. *Pediatric Infectious Disease Journal* 2007; 26(3): 238–242.

Melville-Smith ME, Seagroatt VA and Watkins JT. A comparison of enzyme-linked immunosorbent assay (ELISA) with the toxin neutralisation test in mice as a method for the estimation of tetanus antitoxin in human sera. *J Biol Stand* 1983; 11: 137-44.

Mertsola J, Meeren OVD, He Q et al. Decennial Administration of a Reduced Antigen Content Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine in Young Adults. *Clinical Infectious Diseases* 2010; 51(6):656–662.

Rüggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine* 2007; 25(31): 5675-84.

Ward JI, Cherry JD, Chang SJ, et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. *New England Journal of Medicine* 2005; 353(15): 1555–1563.

Ward JI, Cherry JD, Chang SJ, et al. *Bordetella pertussis* infections in vaccinated and unvaccinated adolescents and adults, as assessed in a national prospective randomised acellular pertussis vaccine trial (APERT), *Clinical Infectious Diseases* 2006; 43(2): 151–157.

WHO National Immunization Coverage Scorecards 2015. 2015a. http://www.who.int/immunization/global_vaccine_action_plan/WHA_Scorecards_DTP_coverage_2014.pdf. Accessed on 02 February 2017.

WHO vaccine-preventable diseases: monitoring system. 2015 global summary. 2015b. http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=RUS&commit=OK. Accessed on 02 February 2017.

Zuckerman JN. The importance of injecting vaccines into muscles. *BMJ* 2000; 321: 1237-38.

# APPENDIX A CLINICAL LABORATORIES

## Table 24 GSK Biologicals' laboratories

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

# APPENDIX B AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

| GlaxoSmithKline Biologicals SA<br>Vaccines R &D<br>**Protocol Amendment 1** | |
|---|---|
| **eTrack study number and Abbreviated Title** | 201532 [DTPA (BOOSTRIX)-050] |
| **IND number** | BB-IND-8461 |
| **EudraCT number** | 2015-003405-42 |
| **Amendment number:** | Amendment 1 |
| **Amendment date:** | 02 February 2017 |
| **Co-ordinating author:** | PPD, Scientific Writer |

**Rationale/background for changes:**

The protocol has been amended to implement the following changes:

- The age at inclusion to study has been changed from 3 to 4 years of age in order to be in compliant with Boostrix's approved EU label wherein it is indicated for booster vaccination in individuals aged four years and older.
- Wording "parents/Legally Acceptable Representative(s) (LAR[s])" is replaced by the wording "parent(s)/adoptive parent(s)". As per Russian legislation, only parents or adoptive parents can give consent for the enrolment of their child in a clinical trial. No other person is allowed to give consent on behalf of a minor to participate in a clinical trial.
- The age groups are amended according to the approved Boostrix EU label and physiological particularities i.e., from 3-9 to 4-9 years (children), 10-19 to 10-17 years (adolescents), 20-64 to 18-64 years (adults) and ≥65 years (elderly population).
- To reflect the upgrade to new version for protocol (15.0), ICF (8.0), eCRF, SPM and overall changes in the functions.
- The inclusion criteria has been amended in order to clarify the following,
  - Children from four to seven years of age who have received diphtheria, tetanus and pertussis vaccination prior to study enrolment as per local recommendations will be enrolled
- Subjects eight years of age and older who have received diphtheria, tetanus and pertussis vaccination to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge and did not receive an additional diphtheria, tetanus or pertussis vaccination within 5 years prior to enrolment in the study will be enrolled.

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

**Title page:**

| | |
|---|---|
| **Detailed Title** | A phase III, open-label, single-group, multi-centre study to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' combined reduced antigen content diphtheria, tetanus and acellular pertussis (dTpa) vaccine, Boostrix™, administered as a booster dose in healthy Russian subjects aged ~~three~~ ***four*** years and older. |
| **Contributing authors** | • PPD, ***Clinical and Epidemiology Project Leader*** ~~Project Level Clinical Research and Development Lead~~<br>• PPD, Clinical Research and Development Lead, contractor for GSK Biologicals<br>• PPD/PPD, Lead Statistician<br>• PPD, Project Statistician<br>• PPD/PPD, Study Delivery Lead<br>• PPD, Study Delivery Manager<br>• PPD, ~~Senior Local Study Manager~~ ***Head of Clinical Operations, Vaccines***<br>• PPD***, Senior Clinical Reserach Associate, Vaccines***<br>• PPD, ~~Vaccine Supply Coordinator,~~ contractor for GSK Biologicals/PPD, ***Clinical Trial Supply Manager***<br>• PPD/PPD, Clinical Read-out Team Leader<br>• PPD, ***Business and Decision Life Sciences contractor for GSK Biologicals***~~CLS Study Manager~~<br>• PPD, Project Data Manager<br>• PPD and PPD/PPD, Study Data Manager<br>• PPD***, Oversight Data Manager***<br>• PPD/PPD, Global Patents Representative<br>• PPD and PPD/PPD ***and*** PPD, Clinical Safety Representatives |

- PPD, Senior Regional Medical Manager
- PPD/PPD, Global Regulatory Affairs

**List of abbreviations:**

| | |
|---|---|
| **ATEAM** | Appropriate (electronic) temperature excursion decision form |
| ~~**ATP**~~ | ~~According To Protocol~~ |
| ~~**eTDF**~~ | ~~Electronic temperature excursion decision form~~ |
| ~~**LAR**~~ | ~~Legally Acceptable Representative~~ |
| **PI** | ~~Product~~ Prescribing Information |

**List of abbreviations:**

| | |
|---|---|
| **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~~. |
| ~~**Legally acceptable representative**~~<br><br>~~**(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 ***(as per Russian legislation, it is parent(s)/adoptive parent(s).***~~ |

**Synopsis**

| | |
|---|---|
| **Indication** | Booster immunisation against diphtheria, tetanus and pertussis diseases of individuals from age of four years onwards. The study population for this study will include individuals aged ~~three~~ ***four*** years and ~~above~~ ***older***. |

**Synopsis and Section 1.2.1 Rationale for the study**

*Boostrix* vaccine contains 0.5 mg Al (as aluminium phosphate and aluminium hydroxide) per 0.5 millilitre (ml) dose. *Boostrix* is currently not registered in Russia. This study will assess the immunogenicity, reactogenicity and safety of *Boostrix* in healthy Russian subjects aged ~~three~~ ***four*** years and older. The data obtained from this study will be used to support the registration of *Boostrix* in Russia for individuals aged ~~3~~ ***4*** years and ***older***~~above~~. ~~Although *Boostrix* is indicated for individuals aged 4 years onwards, in this study, individuals aged 3 years and above have been selected with the intention to increase the coverage rate of the vaccine which may also help reduce the pertussis burden in Russia.~~

**Synopsis and Section 1.2.1 Rationale for the study design**

The study is designed as an open-label, single group trial in which all the study subjects will receive a single dose of *Boostrix* vaccine. An equal number of subjects are expected to be recruited in the following age categories: ***4***~~3~~-9 years ***(children),*** 10-~~19~~ ***17*** years ***(adolescents),*** ~~20~~***18***-64 years ***(adults)*** and ≥65 years ***(elderly population).*** ~~in order to support the registration of *Boostrix* in Russia~~

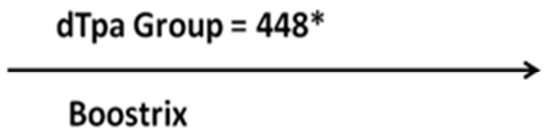
***The ≥65 years (elderly population) has been included in the study to ensure cocooning effect. Pertussis outbreaks have occurred in a number of European and non-European countries. Whilst this resurgence is observed across the age range with a notable increase in cases now being detected in adolescents and older age groups. It is also now recognized that immunity following either natural pertussis infection or vaccination is not long lived, and the acellular pertussis vaccines that have been widely used since the 1990s may be more prone to such waning. Consequently, adults and adolescents with pertussis are a potential source of infection for infants too young to have been fully vaccinated. Many countries recommend 'cocoon ' strategy, i.e. vaccination of family members and close contact of newborn (i.e. grandparents usually above 65 years old), in order to protect infants from acquiring pertussis.***

**Section 1.3. Benefit: Risk Assessment**

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Investigational study vaccine (*Boostrix*)** | | |
| ~~Temperature of ≥ 40.0° C within 48 hours of vaccination, not due to another identifiable cause~~ | ~~As outlined in the RSI from clinical trials and post-marketing safety data, this AE/SAE is recognised as well-characterised identified risks for *Boostrix*.~~ | ~~Subjects/Subjects' parents/legally acceptable representative [LAR(s)] ***adoptive parent*** should report any untoward symptoms experienced, after receiving the vaccine immediately to the investigator.~~ |
| ~~Hypotonic-hyporesponsive episode~~ | ~~As outlined in the *Boostrix* RSI from clinical trials and post-marketing safety data, this AE/SAE is recognised as well-characterised identified risks for *Boostrix*~~ | ~~All SAEs should be reported immediately to GSK. It is important that procedures are in place to avoid injury from fainting. All subjects will need to remain under observation (i.e. visibly followed; no specific procedure) at the vaccination centre for at least 30~~ |

| Important Potential/Identified Risk | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | | ~~minutes after vaccination.~~ |
| ~~Convulsions with or without fever occurring within 3 days of vaccination~~ | ~~As outlined in the *Boostrix* RSI from clinical trials and post-marketing safety data, this AE/SAE is recognised as well-characterised identified risks for the vaccine.~~ | ~~Subjects/Subjects' parents/legally acceptable representative [LAR(s)] ***adoptive parent*** should report any untoward symptoms experienced, after receiving the vaccine immediately to the investigator.~~ |
| ~~Extensive swelling of vaccinated limb~~ | ~~Given that the active ingredients of *Boostrix* are conjugated to tetanus toxoid carrier protein, an exaggerated local (Arthus-like) reaction are occasionally reported following receipt of a diphtheria- or tetanus- containing vaccine. These reactions present as extensive painful swelling, often from shoulder to elbow. They generally begin from 2 to 8 hours after injections and are reported most often in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid.~~ | ~~Subjects/Subjects' parents/legally acceptable representative [LAR(s)] ***adoptive parent*** should report any untoward symptoms experienced, after receiving the vaccine immediately to the investigator.~~ |
| ~~Encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine~~ | ~~As outlined in the *Boostrix* RSI from clinical trials and post-marketing safety data, this AE/SAE is recognised as potential risk for *Boostrix*~~ | ~~Subjects/Subjects' parents/legally acceptable representative [LAR(s)] ***adoptive parent*** should report any untoward symptoms experienced, after receiving the vaccine immediately to the investigator.~~ |
| ~~Adequate human data on use during pregnancy/lactation are not available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development~~ | ~~Monitoring of spontaneous reports~~ | ~~GSK is closely monitoring pregnancy outcomes in spontaneous reports including pregnancy registries~~ |
| **Study Procedure** | | |
| ***Risk from blood sampling.*** | ***Blood sampling associated risk of discomfort, syncope, infection at the site after or during venipuncture*** | ***Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health.*** |

**Synopsis and Section 3. Study design overview**




| Visit: | Visit 1 | Visit 2 |
|---|---|---|
| ~~Time point~~: *Timepoint* | Day ~~0~~ *1* | Day ~~30~~ *31* |
| | Pre-Booster BS | Post-Booster BS |
| | Vaccination | Study End |
| | Age: ≥ ~~3 yrs~~ *4 yrs* | |

~~BS: Blood Sampling~~
* An equal number of subjects are expected to be recruited in the following age categories: ~~3~~*4*-9 years ***(children),*** 10-~~19~~*17* years ***(adolescents),*** ~~20~~*18*-64 years ***(adults)*** and ≥65 years ***(elderly population)*** in order to evaluate data.

**Synopsis and Table 1 Study groups and epochs foreseen in the study**

| Study Groups | Number of subjects* | Age (Min/~~Max~~) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| dTpa Group | 448 | ≥***34*** years | x |

~~* Approximate number~~

Control: uncontrolled ***(in terms of no active comparator***

**Synopsis and Section 4. Study cohort**

Approximately 448 subjects are expected to be enrolled in this study. An equal number of subjects (approximately 112) are expected to be recruited in each of the following age categories: ***4***~~3~~-9 years ***(children),*** 10-~~19~~ ***17*** years ***(adolescents),*** ~~20~~***18***-64 years ***(adults)*** and ≥65 years ***(elderly population)*** in order to evaluate data. Refer to Section 10.1 for a detailed description of criteria used for the estimation of sample size.

**Section 4.2. Inclusion criteria for enrolment**

- Subjects or subjects' parent(s)/***adoptive parent*** ~~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).
- A male or female ~~three~~***four*** years of age and older.
- Written informed assent obtained from subjects aged ~~10~~ ***14*** years to <18 years.

- Written informed consent obtained from the subject/from the parent(s)/***adoptive parent***~~LAR~~(s) of the subject prior to performing any study specific procedure.
- ~~Children three ***four*** to seven years of age who have previously received primary and booster diphtheria, tetanus and pertussis vaccination in the first two years of life, as per local recommendations.~~ Children four to seven years of age who have received diphtheria, tetanus and pertussis vaccination prior to study enrolment as per local recommendations.
- ~~Subjects eight years of age and older who have completed their routine childhood diphtheria, tetanus and pertussis vaccinations to the best of their/subjects' parent(s)/***adoptive parent*** LAR(s) knowledge and as per local recommendations and did not receive a booster dose of the vaccine(s) within 5 years prior to enrolment in the study.~~ Subjects eight years of age and older who have received diphtheria, tetanus and pertussis vaccination to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge and did not receive an additional diphtheria, tetanus or pertussis vaccination within 5 years prior to enrolment in the study will be enrolled.

**Section 4.3. Exclusion criteria for enrolment**

- History of previous or intercurrent diphtheria, tetanus or pertussis diseases since birth in subjects ~~three~~ ***four*** to seven years of age.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the vaccine dose. For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects, ≥18 years of age) or ≥0.5 mg/kg/day (for paediatric subjects, aged ~~3~~***4***-17 years), or equivalent. Inhaled and topical steroids are allowed.

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

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

- Subject/subject's parent(s)/***adoptive parent*** ~~LAR~~(s) informed consent and subject informed assent, as appropriate.

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

**Section 5.2. Subject identification and randomisation**

The enrolment will be performed to ensure equal distribution of the population across the four age strata [***4***~~3~~-9 years ***(children),*** 10-~~19~~ ***17*** years ***(adolescents),*** ~~2~~0***18***-64 years ***(adults)*** and ≥65 years ***(elderly population)***]. Therefore, the expected distribution of subjects is as shown in Table 4.

**Table 4 Number of subjects required for enrolment**

| Age Stratum | Vaccine | N |
|---|---|---|
| ~~4~~***3***-9 years | *Boostrix* | 112 |
| 10-~~19~~ ***17*** years | *Boostrix* | 112 |
| ~~20~~***18***-64 years | *Boostrix* | 112 |
| ≥ 65 years | *Boostrix* | 112 |

N = approximate number of subjects to be enrolled

After obtaining the signed and dated ICF and IAF (if applicable) from the subject and having checked the eligibility of the subject, the study staff in charge of the vaccine administration will access SBIR. Upon providing the age [***~~4~~3***-9 years ***(children),*** 10-~~19~~ ***17*** years ***(adolescents),*** ~~20~~***18***-64 years ***(adults)*** and ≥65 years ***(elderly population)]*** and the subject identification number, the randomisation system will provide the treatment number to be used for the dose.

## Section 5.5. Outline of study procedures

**Table 5 List of study procedures**

| Epoch | Epoch 001 | |
|---|---|---|
| **Type of contact** | **Visit 1** | **Visit 2** |
| **Timepoints** | **Day ~~0~~1** | **Day ~~30~~31** |
| **Sampling timepoints** | **Pre-Bst** | **Post-Bst** |
| Recording of solicited adverse events within 4 days (Day 1–4) post-vaccination by subjects/subjects' parent(s)/***adoptive parent*** ~~LAR~~(s) | ● | |
| Recording of non-serious adverse events within 31 days (Day 1-31) post-vaccination, by subjects/subjects' parent(s)/***adoptive parent*** ~~LAR~~(s) | ● | ● |

● 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.
# Physical examination after the vaccination visit, will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.
Pre-Bst: Before the administration of study vaccine; Post-Bst: one month after the administration of study vaccine.
[1] Applicable to women of child-bearing potential
[2] Refer to the table notes under Table 12 for a detailed explanation on the reporting of large injection site reactions by the subject's/subjects' parent(s)/***adoptive parent*** ~~LAR~~(s).

## Section 5.6.1. Informed consent

The signed/witnessed informed consent of the subject/subject's parent(s)/***adoptive parent ~~LAR~~***(s) must be obtained before study participation. The signed informed assent of the subject below the age of consent (i.e. minor) should be obtained in addition to the signed informed consent by his/her parent(s)***/adoptive parent ~~LAR~~***(s) according to local rules and regulations. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

**Section 5.6.4. Medical history and vaccination history**

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

Review the subject's childhood diphtheria, tetanus and pertussis vaccinations to collect information on the vaccine name, route of administration, dose number and date of administration***.*** This information should be recorded in the eCRF.

**Section 5.6.9.1 Blood sampling for antibody determination**

- A volume of approximately 5 ml of whole blood (to provide approximately 1.7 ml of serum) should be drawn from all subjects ~~included in the immunogenicity analysis of humoral immune response~~ at the pre-booster and post-booster timepoint (Visit 1 and Visit 2). After centrifugation, serum samples should be kept at –20°C or below until shipment.

**Section 5.6.12. Distribution of diary cards and recording of AEs, SAEs, and pregnancies**

- The subjects/subjects' parent(s)/***adoptive parent ~~LAR~~***(s) will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.
- At Visit 1, diary cards will be provided to the subject/subject's parent(s)/***adoptive parent ~~LAR~~*** (s). The subject/subject's parent(s)/***adoptive parent ~~LAR~~***(s) will record body (preferably 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/subject's parent(s)/***adoptive parent ~~LAR~~***(s) will be instructed to return the completed diary card to the investigator at the next study visit.
  - Note: Diary cards can be filled in by a minor subject under the supervision of the subject's parent(s)/***adoptive parent ~~LAR~~***(s) provided that the minor has the competency to assess and report the information to be provided in the diary card. The ultimate accountability for the completion of the diary cards remains with the subject's parent(s)/***adoptive parent ~~LAR~~*** (s). The investigator should discuss this accountability with the subject's parent(s)/***adoptive parent ~~LAR~~*** (s).
- Collect and verify completed diary cards during discussion with the subject/subject's parent(s)/***adoptive parent ~~LAR~~***(s) on Visit 2.
  - Note: If the diary card has been filled in by a minor subject, the investigator or delegate should verify the reported information during a discussion with the minor subject preferably in the presence of his/her parent(s)/***adoptive parent ~~LAR~~***(s).
- After vaccination, if the subjects or the subject's parents/***adoptive parent ~~LAR~~*** observe any large injection site reaction (defined as a swelling with a diameter of > 50 mm for subjects <6 years of age and >100 mm for subjects ≥6 years of age,

noticeable diffuse swelling or noticeable increase in limb circumference) during the 4-day follow-up (Day 1-4) period, they will be asked to contact study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator will record detailed information describing the AE on a specific large injection site reaction screen in the eCRF.

**Section 5.6.13. Return of diary card and diary card transcription**

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

**Section 5.6.14. Recording of AEs, SAEs and pregnancies**

- The subjects/subjects' parent(s)/***adoptive parent*** ~~LAR~~(s) will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.

**Section 5.7. Biological sample handling and analysis**

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

**Section 6.1. Description of Study vaccine**

~~*Boostrix* is indicated for booster immunisation against diphtheria, tetanus and pertussis diseases of individuals aged four years and above. However, in this study, the study population will include individuals aged three years and above. This age has been selected with the intention to increase the coverage rate of the vaccine which may also help reduce the pertussis burden in Russia which was estimated at about 4,705 cases per 100,000 population in 2014 [WHO, 2015b].~~

**Section 6.2. Storage and handling of study vaccine**

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) or above -15.0°C (for -20°C/-4°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form (***ATEAM*** ~~[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 ***ATEAM***, 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.

**Section 6.7. Concomitant medications/products and concomitant vaccinations**

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

**Section 6.7.1. Recording of concomitant medications/products and concomitant vaccinations**

- 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 ***in eCRF***.

~~*SAEs that are required to be reported per protocol.~~

**Section 8. Safety**

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

**Section 8.1.3.1. Solicited local (injection site) adverse events**

Note: If the subjects or the subject's parent(s)/***adoptive parent*~~LAR~~(s) observe any large injection site reaction (defined as a swelling with a diameter of >50 mm for subjects <6 years of age and >100 mm for subjects ≥6 years of age, noticeable diffuse swelling or noticeable increase in limb circumference) during the 4-day (Day 1–4) follow-up period after vaccination, they will be asked to contact the study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator will record detailed information describing the AE on a specific large injection site reaction sheet in the eCRF.

**Section 8.1.3.2. Solicited general adverse events**

**Table 13 Solicited general adverse events**

| Toddler/Child (<6 years) |
|---|
| Drowsiness |
| Fever |
| Irritability/Fussiness |
| Loss of appetite |

| Adult/Child (≥6 years) |
|---|
| Fatigue |
| Fever |
| Gastrointestinal symptoms † |
| Headache |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

Subjects/parent(s)/***adoptive parent***~~LAR~~(s) will be instructed to measure and record the ~~axillary, rectal or oral~~ body temperature ***by axillary route*** in the evening. Should additional temperature measurements be performed at other times of day, subjects/parent(s)/***adoptive parent***~~LAR~~(s) will be instructed to record the highest temperature in the diary card.

**Section 8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies**

***All pregnancies recorded during this period will be followed up as detailed in section 8.2,***~~See section~~ 8.4 ~~for instructions on reporting of pregnancies.~~***and 8.5.2.***

**Table 14 Reporting periods for collecting safety information**

| Event | Pre-Bst (consent obtained) | Vaccination (Day 1) | ~~4 days~~ Post Bst (Day 1-4) | ~~31 days~~ Post Bst (Day1-31) ~~Study Conclusion~~ |
|---|---|---|---|---|
| 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/vaccination | | | | |
| Pregnancies* | | | | |

Pre-Bst: Before the administration of study vaccine; Post-Bst: one month after the administration of study vaccine.
***This refers to collecting information on pregnancy as an event and not as an outcome, which will be collected after the end of the study.***

**Section 8.3.3.1. Active questioning to detect adverse events and serious adverse events**

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

**Section 8.3.3.2.1**

**Table 15 Intensity scales for solicited symptoms in children less than 6 years of age**

| ***Toddler*/Child (< 6 years)** | | |
|---|---|---|
| **Adverse Event** | **Intensity grade** | **Parameter** |
| Pain at injection site | 0 | None |
| | 1 | Mild: Minor reaction to touch |
| | 2 | Moderate: Cries/protests on touch |
| | 3 | Severe: Cries when limb is moved/spontaneously painful |

**Table 16 Intensity scales for solicited symptoms in adults and children of 6 years of age or more**

| Adults/Child (≥ 6 years) | | |
|---|---|---|
| **Adverse Event** | **Intensity grade** | **Parameter** |
| Pain at injection site | 0 | None |
| | 1 | Mild: Any pain neither interfering with nor preventing normal every day activities. |
| | 2 | Moderate: Painful when limb is moved and interferes with every day activities. |
| | 3 | Severe: Significant pain at rest. Prevents normal every day activities. |

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

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

| | | |
|---|---|---|
| 3 (severe) | = | An AE which prevents normal, everyday activities.<br><br>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)/***adoptive parent***~~LAR~~(s) to seek medical advice. In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy. |

**Section 8.7. Subject card**

Study subjects/subjects' parent(s)/***adoptive parent***~~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/subject's parent(s)/***adoptive parent***~~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/subjects' parent(s)/***adoptive parent***~~LAR~~(s) must be instructed to keep subject cards in their possession at all times during the study duration.

**Section 9.2.1. Subject withdrawal from the study**

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 himself/herself, by the subject's parent(s)/***adoptive parent***~~LAR~~(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

**Section 10.3. Determination of sample size**

According to Russian regulations, for the purpose of product registration, the minimum sample size required is 100 subjects in each age group. Therefore, the total number of evaluable subjects is 400 [100 subjects in each age group, ***4***~~3~~-9 years (***children),*** 10-~~19~~ ***17*** years ***(adolescents),*** ~~20~~***18***-64 years ***(adults)*** and ≥65 years ***(elderly population***)]. Assuming a drop-out rate of 10%, to compensate for subject attrition due to early withdrawal, a total of 448 subjects (112 in each age group) will be enrolled in to the study in order to obtain the desired number of evaluable subjects for analysis.

**Section 10.6. Analysis of demographics**

**Table 23 Age stratification**

| Age groups | Number of subjects |
|---|---|
| ***4***~~3~~-9 years | ~112 |
| 10-~~19~~***17*** years | ~112 |
| ~~20~~***18***-64 years | ~112 |
| ≥65 years | ~112 |

# GlaxoSmithKline Biologicals SA

Vaccines R &D

## Protocol Amendment 2

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 201532 [DTPA (BOOSTRIX)-050] |
| **IND number** | BB-IND-8461 |
| **EudraCT number** | 2015-003405-42 |
| **Amendment number:** | Amendment 2 |
| **Amendment date:** | 07 August 2017 |
| **Co-ordinating author:** | PPD , Scientific Writer |

**Rationale/background for changes:**

This protocol amendment was developed after the comments from the Russian regulatory authorities [Ministry of Health (MoH)]. Adjustments to the text were made in certain sections for better readability and to clarify the inclusion and exclusion criteria for enrolment of subjects and the conduct of the study. In addition, adjustments for the reporting period and assessment of adverse events in the safety sections were made for consistency. Typos and errors were corrected throughout the document. The newly re-developed and re-validated GSK's DTPa ELISA cut-offs were updated as per the most recent CBER recommendation (2017).

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

**Title page:**

**Contributing authors**

- PPD ***, Clinical Research and Development Lead***
- PPD , ~~Senior Local Study Manager~~ ***Head of Clinical Operations***, Vaccines
- PPD , Senior Clinical ~~Reserach~~ ***Research*** Associate, Vaccines



**Synopsis:**

**Rationale for the study and study design**

Studies have shown that childhood pertussis burden can be significantly reduced by vaccination of adolescents and adults [Ward, 2005; Ward, 2006]. Hence, boosting with reduced-antigen-content diphtheria and tetanus toxoids and acellular pertussis vaccine (dTpa) instead of ~~DT~~***dT*** may prolong the immunity against pertussis infection.

~~The ≥ 65 years (elderly population) has been included in the study to ensure cocooning effect.~~ Pertussis outbreaks have occurred in a number of European and non-European countries. ~~Whilst t~~***This*** resurgence is observed across the age range with a notable increase in cases now being detected in adolescents and older age groups. It is also now recognised that immunity following either natural pertussis infection or vaccination is not long lived, and the acellular pertussis vaccines that have been widely used since the 1990s may be more prone to such waning. Consequently, adults and adolescents with pertussis are a potential source of infection for infants too young to have been fully vaccinated. Many countries recommend 'cocoon ' strategy, i.e. vaccination of family members and close contact of newborn (i.e. grandparents usually above 65 years old), in order to protect infants from acquiring pertussis. ***The ≥65 years (elderly population) have therefore been included in the study***.

**Study design**

- Experimental design: Phase III, open-label, non-randomised, multi-centric, single-country study with a single group.
- Duration of the study:
  - Epoch 001: Primary ***Epoch*** starting at Visit 1 (Day 1) and ending at Visit 2 (Day 31)

- Primary Completion Date (PCD): Visit 2 (Day 31)
- End of Study (EoS): Last testing results released of samples collected at Visit 2
- Study groups: dTpa group: Subjects aged four years and older

**Synopsis Table 4 Study groups and epochs foreseen in the study**

| Study Groups | Number of subjects* | Age (Min) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| dTpa Group | 448 | ≥4 years | x |

**List of abbreviations**

| | |
|---|---|
| ***dT:*** | ***Reduced-antigen-content diphtheria and tetanus toxoid vaccine*** |
| ***ELISA:*** | ***Enzyme-linked immunosorbent assay*** |
| ***IAF:*** | ***Inform Assent Form*** |
| ***IB*** | ***Investigator Brochure*** |
| ***ICF:*** | ***Inform Consent Form*** |
| ~~**PI:**~~ | ~~Prescribing Information~~ |

**Trademarks:**

| Trademark of the G*S*~~laxoSmithKline~~ group of companies | Generic description |
|---|---|
| *Boostrix* | Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (dTpa) vaccine |

**Section 1.2.1: Rationale for the study**

Studies have shown that childhood pertussis burden can be significantly reduced by vaccination of adolescents and adults [Ward, 2005; Ward, 2006]. Hence, boosting with reduced-antigen-content diphtheria and tetanus toxoids and acellular pertussis vaccine (dTpa) instead of diphtheria and tetanus toxoids (~~D~~***dT***) may prolong the immunity against pertussis infection.

**Section 1.2.2: Rationale for the study design**

~~The ≥ 65 years (elderly population) has been included in the study to ensure cocooning effect.~~ Pertussis outbreaks have occurred in a number of European and non-European countries. ~~Whilst t~~***This*** resurgence is observed across the age range with a notable increase in cases now being detected in adolescents and older age groups. It is also now recognized that immunity following either natural pertussis infection or vaccination is not long lived, and the acellular pertussis vaccines that have been widely used since the

1990s may be more prone to such waning. Consequently, adults and adolescents with pertussis are a potential source of infection for infants too young to have been fully vaccinated. Many countries recommend 'cocoon ' strategy, i.e. vaccination of family members and close contact of newborn (i.e. grandparents usually above 65 years old), in order to protect infants from acquiring pertussis. ***The ≥65 years (elderly population) have therefore been included in the study***.

**Section 1.3: Benefit: Risk Assessment**

Please refer to the ~~Prescribing information (PI)~~ ***current Investigator Brochure (IB)*** for the summary of the potential risks and benefits of *Boostrix*.

**Section 3: Study design and overview**

- Duration of the study:
  - Epoch 001: Primary ***Epoch*** starting at Visit 1 (Day 1) and ending at Visit 2 (Day 31)

**Section 4.2: Inclusion criteria for enrolment**

- ~~Children ***four*** to seven years of age who have received diphtheria, tetanus and pertussis vaccination prior to study enrolment as per local recommendations.~~
- ***Children 4-7 years of age with documented previous diphtheria, tetanus and pertussis vaccination (primary series and first booster) as per local recommendation prior to study enrolment, but should have not received any further diphtheria-tetanus containing booster planned at 6-7 years of age as per local recommendations or any other diphtheria, tetanus and pertussis containing vaccine.***

  **OR**

- Subjects eight years of age and older who ~~have received~~ ***can report previous*** diphtheria, tetanus and pertussis vaccination – ***documented or*** to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge – and did not receive an additional diphtheria, tetanus or pertussis vaccination within five years prior to enrolment in the study will be enrolled.

**Section 4.3: Exclusion criteria for enrolment**

- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after the dose of vaccine with the exception of inactivated influenza vaccine which can be given at any time during the study conduct as per the Summary of Product Characteristics (SmPC) ~~or PI~~ and according to the local governmental recommendations.
- Acute or chronic, clinically significant ***uncontrolled*** pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination***, and/***or laboratory screening tests.

**Section 5.3: Method of blinding**

This is an open-label study as all the subjects will receive a booster dose of *Boostrix*.

~~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.~~

**Table 5: Footnote**

Physical examination after the vaccination visit, will be performed only if the subject***/subject's parent(s)/adoptive parent(s)*** indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

**Section 5.6.4: Medical history and vaccination history**

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

Review the subject's***** childhood diphtheria, tetanus and pertussis vaccinations to collect information on the vaccine name, route of administration, dose number and date of administration. This information should be recorded in the eCRF.

****For subjects eight years and older, with no documented previous diphtheria, tetanus and pertussis vaccinations, details are to be recorded to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge.***

**Section 5.6.12: Distribution of dairy cards and recording of AEs, SAEs and pregnancies**

- Refer to Section 8.3 for procedures for the investigator ***or delegate*** to record AEs, SAEs, and pregnancies. Refer to Section 8.4 for guidelines and how to report SAE, and pregnancy reports to GSK Biologicals.
- The subjects/subjects' parent(s)/adoptive parent (s) will be instructed to contact the investigator ***or delegate*** immediately should they/the subjects manifest any signs or symptoms they perceive as serious.
- At Visit 1, diary cards will be provided to the subject/subject's parent(s)/adoptive parent(s). The subject/subject's parent(s)/adoptive parent(s) will record body (preferably axillary) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next three days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days) occurring after vaccination. The subject/subject's parent(s)/adoptive parent(s) will be instructed to return the completed diary card to the investigator ***or delegate*** at the next study visit.
  - Note: Diary cards can be filled in by a minor subject under the supervision of the subject's parent(s)/adoptive parent(s) provided that the minor has the competency to assess and report the information to be provided in the diary card.

The ultimate accountability for the completion of the diary cards remains with the subject's parent(s)/adoptive parent(s). The investigator ***or delegate*** should discuss this accountability with the subject's parent(s)/adoptive parent(s).

- After vaccination, if the subjects or the subject's parents/adoptive parents observe any large injection site reaction ***(***~~defined as a swelling with a diameter of >50 mm for subjects <6 years of age and >100 mm for subjects ≥6 years of age~~ ***for subjects <6 years of age defined as a swelling with a diameter of >50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm***, noticeable diffuse swelling or noticeable increase in limb circumference) during the 4-day follow-up (Day 1-4) period, they will be asked to contact study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator ***or delegate*** will record detailed information describing the AE on a specific large injection site reaction screen in the eCRF.

Throughout the document for the procedures for the investigator, "**or delegate**" was added as appropriately.

**Section 5.6.13: Return of dairy card and dairy card transcription**

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

**Section 5.6.14: Recording of AEs, SAEs and pregnancies**

- Refer to Section 8.3 for procedures for the investigator ***or delegate*** to record AEs, SAEs, pregnancies. Refer to Section 8.4 for guidelines and how to report SAE and pregnancy reports to GSK Biologicals.
- The ***subject***/subjects' parent(s)/adoptive parent(s) will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.

**Section 5.7.3: Laboratory assays**

***All serology will be determined in GSK Biologicals' laboratories or in a laboratory designated by GSK using standardized and validated procedures with adequate controls.***

***Refer to Table 8 for the assays used in antibody determination.***

## Table 8 Humoral Immunity (Antibody determination)

| System | Component | Method | Kit / Manufacturer | Unit | Cut-off† | Laboratory* |
|---|---|---|---|---|---|---|
| Serum | *Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG* | ELI | NA | IU/ml | ***0.057***~~.1~~ | GSK Biologicals or designated laboratory |
| Serum | *Corynebacterium diphtheriae.Diphtheria Toxoid Ab* | NEU assay on Vero cells** | NA | IU/ml | 0.004 | GSK Biologicals or designated laboratory |
| Serum | *Clostridium tetani.Tetanus Toxoid Ab.IgG* | ELI | NA | IU/ml | ***0.043***~~.1~~ | GSK Biologicals or designated laboratory |
| Serum | *Bordetella pertussis.Pertactin Ab.IgG* | ELI | NA | ***IU/ml*** ~~EU/ml$~~ | ***2.693***~~5~~ | GSK Biologicals or designated laboratory |
| Serum | *Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG* | ELI | NA | ***IU/ml*** ~~EU/ml$~~ | ***2.046***~~5~~ | GSK Biologicals or designated laboratory |
| Serum | *Bordetella pertussis.Pertussis Toxin Ab.IgG* | ELI | NA | ***IU/ml*** ~~EU/ml$~~ | ***2.187***~~5~~ | GSK Biologicals or designated laboratory |

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

## Section 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 ***newly validated*** assay cut-off for anti-diphtheria is currently set at ~~0.1 IU/ml (ELISA)~~***0.057 IU/ml*** and ***for*** anti-tetanus ***at 0.043 IU/ml. For both serology a threshold of 0.1 IU/ml*** ~~which~~ provides a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983].
- The cut-off of the Vero-cell ***neutralisation*** assay (performed for pre- and post-vaccination serum samples when ELISA ***anti-diphtheria*** antibody concentrations are <0.1 IU/ml) is 0.004 IU/ml. Antibody concentrations ≥0.01 IU/ml are considered as protective [Camargo, 1984]. The ELISA test will define the seroprotection status for the primary endpoint.

- No ***serological*** correlate of protection is defined for the immune response to pertussis antigens. Antibodies against the pertussis components PT, FHA and PRN will be measured by ELISA technique. ~~The current cut-off for all three pertussis antibody assay is 5 ELISA Units per ml (EL.U/ml)~~. ***The newly validated assay cut-off for anti-PT is 2.693 IU/ml, for anti-FHA is 2.046 IU/***ml ***and for anti-PRN is 2.187 IU/ml.*** Subjects with antibody concentration below this cut-off will be considered seronegative. ~~[Granstrom, 1987; Karpinsky, 1987].~~

Non-responders are defined as:

- Antibody concentrations <0.01 IU/ml post-booster for diphtheria antigen by Vero-cell ***neutralisation*** assay and,
- Antibody concentrations <0.1 IU/ml post-booster for tetanus antigen by ELISA assay

**Section 6.3: Dosage and administration of study vaccine**

The vaccine will be administered as an IM injection into the deltoid muscle of the non-dominant arm, i.e. in the left arm if the subject is right-handed or in the right arm if the subject is left-handed. ***In case it is not possible for a valid reason to inject in the non-dominant arm, an injection in the dominant arm may be performed.*** *Boostrix* should in no circumstances be administered intravascularly.

**Section 6.5: Contraindications to vaccination**

Since this is a single dose study, contraindications to vaccination are included in the exclusion criteria. Refer to Section 4.3.

~~The following events constitute contraindications to further administration of *Boostrix*. 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 8.5).~~

***The following events constitute contraindications to administration of Boostrix at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 6.7.1), or the subject may be withdrawn at the discretion of the investigator (see Section 6.7.2).***

**Section 6.6: Warnings and precautions**

~~Refer to the package insert of *Boostrix*.~~ ***As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after vaccination.***

***Boostrix vaccination should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular (IM) administration to these subjects.***

***Boostrix vaccination should under no circumstances be administered intravenously.***

**Section 6.7.2: Concomitant medications/products/vaccines that may lead to the elimination of a subject from per protocol 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, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics (SmPC) ~~or PI~~ and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

**Section 8.1.3.1: Solicited local (injection-site) adverse events**

Note: If the subjects or the subject's parent(s)/adoptive parent(s) observe any large injection site reaction ~~(defined as a swelling with a diameter of > 50 mm for subjects <6 years of age and >100 mm for subjects ≥6 years of age,~~ ***for subjects <6 years of age defined as a swelling with a diameter of > 50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm***, noticeable diffuse swelling or noticeable increase in limb circumference) during the 4-day (Day 1–4) follow-up period after vaccination, they will be asked to contact the study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator ***or delegate*** will record detailed information describing the AE on a specific large injection site reaction sheet in the eCRF.

**Section 8.2.1: Pregnancy**

Furthermore, any SAE occurring as a result of a post-study pregnancy and considered by the investigator to be reasonably related to the study vaccine will be reported to GSK Biologicals as described in Section 8.4.3. While the investigator ***or delegate*** is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

**Section 8.3.1: Time period for detecting and recording adverse events, serious adverse events and pregnancies**

All AEs starting within ~~three~~ ***30*** days following administration of the dose of study vaccine (~~Day 1–4~~ Day 1-***31***) must be recorded onto the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

**Section 8.3.2: 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 14. Investigator***(s) or delegate(s) is/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 8.3.3.1: Active questioning to detect adverse events and serious adverse events**

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 ***or delegate*** will then record all relevant information regarding an AE/SAE in the eCRF. The investigator ***or delegate*** 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.

**Section 8.3.3.2.1: Assessment of intensity**

The maximum intensity of fever 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~~ |
| 0 | = | ***<38 °C*** |
| 1 | = | ***≥38.0 °C to ≤39.0 °C*** |
| 2 | = | ***>39.0 °C to ≤40.0 °C*** |
| 3 | = | ***>40.0 °C*** |

**Section 8.3.3.2.2: Assessment of causality**

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 study vaccine will be considered and investigated. The investigator will also consult the IB and/or SmPC ~~and/or PI~~ for marketed products to determine his/her assessment.

**Section 8.4.3: 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 ***or delegate*** does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

**Section 9.2.1: Subject withdrawal from the study**

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

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

**Section 10.5: Derived and transformation data**

- A seroprotected subject is a subject whose antibody concentration is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-~~D~~diphtheria antibody concentrations ≥~~ assay cut-off~~ ***0.1 IU/ml.***
  - Anti-~~T~~tetanus antibody concentrations ≥~~ assay cut-off~~ ***0.1 IU/ml.***
- Booster response to D***iphtheria*** and T***etanus*** antigens is defined as:
  - for ~~initially seronegative~~ subjects ***with*** pre-vaccination ***antibody*** concentration ***<0.1 IU/ml (i.e. below the seroprotection cut-off)*** ~~(pre-vaccination concentration below assay cut-off)~~***,*** antibody concentrations at least ~~four times the assay cut-off~~ ***≥0.4 IU/***ml***,*** one month after vaccination, and
  - for ~~initially seropositive~~ subjects ***with*** pre-vaccination ***antibody*** concentration ***≥0.1 IU/ml (i.e. equal or above the seroprotection cut-off),*** an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- Booster response to PT, FHA and PRN antigens is defined as:
  - for subjects with pre-vaccination antibody concentration below ~~(i.e. <)~~ the assay ***cut-off***, post-vaccination concentration ≥ four times the assay ***cut-off***,
  - for subjects with pre-vaccination antibody concentration between the assay ***cut-off*** and below ~~(i.e.)~~ four times the assay ***cut-off***, post-vaccination antibody concentration ≥ four times the pre-vaccination ***antibody*** concentration, and
  - for subjects with pre-vaccination antibody concentration ≥ four times the assay ***cut-off***, post-vaccination antibody concentration ≥ two times the pre-vaccination ***antibody*** concentration.

**Section 10.7: Analysis of immunogenicity**

- Booster response rate one month post-vaccination will be calculated with exact 95% CIs for ***diphtheria, tetanus and*** pertussis antigens.

**Section 10.8: Analysis of safety**

The ~~overall incidence~~ ***percentage of subjects*** with at least one local symptom (solicited or unsolicited), with at least one general symptom (solicited or unsolicited) and with any symptom (solicited or unsolicited) during the 4-day (Day 1-4) follow-up period after booster vaccination will be tabulated with exact 95% CI after booster vaccination.

Any large injection site reaction ~~(defined as a swelling with a diameter of >50 mm for subjects <6 years of age and >100 mm for subjects ≥6 years of age~~ ***for subjects <6 years***

***of age defined as a swelling with a diameter of > 50 mm and for subjects ≥6 years of age swelling with a diameter of >100 mm***, noticeable diffuse swelling or noticeable increase in limb circumference) onset during the 4-day (Day 1-4) follow-up period after vaccination will be described in detail.

## Section 13: Reference

~~Granström M, Thoren M, Blennow M, et al. Acellular Pertussis Vaccine in Adults: Adverse Reactions and Immune Response. *Eur J Clin Microbiol* 1987;6(1):18-21.~~

~~Karpinsky KF, Hayward S and Tryphonas H. Statistical considerations in the quantitation of serum immunoglobulin levels using the enzyme-linked immunosorbent assay (ELISA). *J Immunol Methods,* 1987; 103: 189-94.~~

## Appendix A: Clinical Laboratories

**~~Table 26 Outsourced Laboratories~~**

| ~~Laboratory~~ | ~~Address~~ |
|---|---|
| ~~NÉOMED-LABS Inc *(formerly GSK GVCL Laval)*~~ | ~~525, Blvd Cartier Ouest Laval Quebec Canada CH7V 3S8~~ |
| ~~Q² Solutions~~ | ~~Unit B1, Parkway West Industrial Estate Cranford Lane – Heston, Middlesex TW5 9Q4 UK~~ |

**Throughout the document 100.4°F was removed since the scale Fahrenheit is not used for measuring temperature in Russia.**

# GlaxoSmithKline Biologicals SA

Vaccines R &D

## Protocol Amendment 3

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 201532 [DTPA (BOOSTRIX)-050] |
| **IND number** | BB-IND-8461 |
| **EudraCT number** | 2015-003405-42 |
| **Amendment number:** | Amendment 3 |
| **Amendment date:** | 31 October 2017 |
| **Co-ordinating author:** | PPD , Scientific Writer |

**Rationale/background for changes:**

This protocol amendment was developed in order to accommodate older adults (approximately 58 years old and older) who were born before national recommendations in Russia for infant DTP vaccination. The protocol amendment will also clarify inconsistencies present in the Protocol Amendment 2, between the English version and the Russian version. Following which, adjustments to the text were made in the inclusion criteria to clarify the enrolment of subjects for age group eight years and above.

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

**Protocol Amendment 3 Investigator Agreement**

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~~ ***parent(s)/adoptive parent(s)***.

**Section 4.2: Inclusion criteria for enrolment**

Subjects eight years of age and older who can report previous diphtheria, tetanus ~~and~~ ***with or without*** pertussis vaccination – documented or to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge – and did not receive an additional diphtheria, tetanus ***with*** or ***without*** pertussis vaccination within five years prior to enrolment in the study will be enrolled.

**Section 5.1: Regulatory and ethical considerations, including the informed consent process**

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, those subjects who can only be enrolled in the study with the consent of the subject's ***parent(s)/adoptive parent(s)*** ~~legally acceptable representative~~ (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and, if

capable, the subject should sign and personally date a written informed assent form (IAF). It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by his/her legal representative. It should be assessed whether an assent is required depending of the age of the study population and the local requirements.

**Section 5.6.4: Medical history and vaccination history**

Review the subject's* childhood diphtheria, tetanus***, with or without*** ~~and~~ pertussis**,** vaccinations to collect information on the vaccine name, route of administration, dose number and date of administration. This information should be recorded in the eCRF.

*For subjects eight years and older, with no documented previous diphtheria, tetanus**, with or without*** ~~and~~ pertussis**,** vaccinations, details are to be recorded to the best of their/subjects' parent(s)/subjects' adoptive parent(s) knowledge.

**Section 5.7.3: Laboratory assays (Table 8: footnote)**

***ELISA's*** ~~Assays~~ for diphtheria, tetanus and pertussis were re-developed and re-validated as per most recent CBER recommendations (Guidance for Industry "Bioanalytical Method Validation" from September 2013). The new assay cut-off's that apply are listed in the table. ***The neutralisation assay for Diphtheria is still under re-development and the assay cut-off might be subject to change during the course of the study. In this case, it will be documented in the clinical study report.***

**Section 5.7.5: Immunological correlates of protection**

The cut-off of the Vero-cell neutralisation assay (performed for pre- and post-vaccination serum samples when ELISA anti-diphtheria antibody concentrations are <0.1 IU/ml) is 0.004 IU/ml. Antibody concentrations ≥0.01 IU/ml are considered as protective [***WHO, 1994*** ~~Camargo, 1984~~]. ***Both, the*** ELISA test ***(antibody concentrations ≥0.1 IU/ml) and Vero-cell test (antibody concentrations ≥0.01 IU/ml)*** will define the seroprotection status for the primary endpoint.

**Section 10.5: Derived and transformed data**

Anti-diphtheria antibody concentrations ≥0.1 IU/ml ***for ELISA assay and ≥0.01 IU/ml for Vero-cell assay.***

**Section 13: References**

***Efstratiou A. & Maple P.A.C., 1994. Diphtheria. Laboratory diagnosis of Diphtheria. The expended programme on immunization in the European region of WHO. WHO ICP/EPI 038 (C). World Health Organization, Geneva, Switzerland.***