TITLE PAGE

Protocol Title: A phase IV, single-blind, randomised, controlled, multi-country study to evaluate the immunogenicity and safety of GSK's *Infanrix hexa* (DTPa-HBV-IPV/Hib) versus MCM Vaccine BV's *Vaxelis* (DTaP5-HBV-IPV-Hib), when administered intramuscularly according to a 2-, 4- and 12-month schedule in healthy infants and toddlers

Protocol Number: 212645

Amendment Number: 1

Product: GlaxoSmithKline Biologicals SA's (GSK) diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and *Haemophilus influenzae* type b conjugate vaccine (DTPa-HBV-IPV/Hib) (GSK-217744, *Infanrix hexa*)

Short Title: A Phase IV study to evaluate immunogenicity and safety of GSK's *Infanrix hexa* (DTPa-HBV-IPV/Hib) versus MCM Vaccine BV's *Vaxelis* (DTaP5-HBV-IPV-Hib) in healthy infants and toddlers

Study Phase: IV

Sponsor Name: GlaxoSmithKline Biologicals SA

Legal Registered Address: Rue de l'Institut, 89, 1330 Rixensart, Belgium

Regulatory Agency Identifying Number(s):

EudraCT: 2019-002988-10

Date of Protocol: 06 April 2021

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

PPD

2 April 2021

Nadia Meyer, MD
Clinical and Epidemiology R&D Project Leader
GlaxoSmithKline Biologicals SA

Date

Medical Monitor name and contact information can be found in Appendix 2.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document History

Document	Date	Substantial	Region
Amendment 1	06 Apr 2021	No	Global
Original Protocol	21 Feb 2020	-	-

Amendment 1 (06 April 2021)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the study.

Overall Rationale for the Amendment:

This amendment was made to clarify when to collect information regarding concomitant therapies and vaccines, and which therapies and vaccines must be recorded on the eCRF. In addition, there were minor editorial changes.

Table 2 Description of Changes in Amendment

Section # and Name	Description of Change	Brief Rationale
Synopsis, and 3.0, Objectives and Endpoints	Added "≥" to secondary objective, preceding each number: "To assess the immunogenicity of Hib-components in terms of percentage of subjects above the thresholds for short-term (≥0.15 µg/mL) and long-term (≥1.0 µg/mL) protection…"	Editorial
6.6, Concomitant Therapy	More detailed information regarding concomitant therapies and vaccines and which therapies or vaccines to record on eCRF	Clarification

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase IV, single-blind, randomised, controlled, multi-country study to evaluate the immunogenicity and safety of GSK's *Infanrix hexa* (DTPa-HBV-IPV/Hib) versus MCM Vaccine BV's *Vaxelis* (DTaP5-HBV-IPV-Hib), when administered intramuscularly according to a 2-, 4- and 12-month schedule in healthy infants and toddlers

Short Title: A phase IV study to evaluate immunogenicity and safety of GSK's *Infanrix hexa* (DTPa-HBV-IPV/Hib) versus MCM Vaccine BV's *Vaxelis* (DTaP5-HBV-IPV-Hib) in healthy infants and toddlers

Rationale:

Aside from *Infanrix hexa*, 2 other hexavalent combination vaccines are currently available: *Hexyon/Hexacima/Hexaxim*™ (registered by Sanofi Pasteur in 2013) and *Vaxelis*™ (registered by MCM Vaccine BV in 2016). Available data from the clinical development of *Vaxelis* show numerical differences in the *Haemophilus influenzae* type b (Hib) immune response between *Infanrix hexa* and *Vaxelis* vaccines following the primary vaccination in infants; more specifically a higher anti-polyribosylribitol phosphate (anti-PRP) antibody response was demonstrated after *Vaxelis* as compared to *Infanrix hexa*. However, the observed anti-PRP geometric mean concentrations (GMCs) following *Vaxelis* booster dose in toddlers was lower as compared to *Infanrix hexa* booster dose increase. This study is intended to show both the non-inferiority of *Infanrix hexa* versus *Vaxelis*, as well as the superiority of *Infanrix hexa* versus *Vaxelis* in terms of anti-PRP GMCs and proportion of subjects with antibody concentrations above a threshold of 5 µg/mL 1 month after the booster dose.

Objectives and Endpoints

Objectives	Endpoints
Co-primary	
Confirmatory 1.To demonstrate that the Hib response in the Investigational Group (Inv_group) is non-inferior to the Comparator Group (Com_group), 1-month post-booster vaccination in terms of: • GMCs o *Criterion: Lower limit (LL) of the 2-sided 95% confidence interval (CI) on group GMC ratio (Inv_group over Com_group) is above 0.5.* • Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL. o *Criterion: First primary objective is met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above -10%.* 2. To demonstrate that the Hib response in Inv_group is superior to Com_group, 1-month post-booster vaccination in terms of: • GMCs o *Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group GMC ratio (Inv_group over Com_group) is above 1.* • Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL. o *Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above 0.* Note: A hierarchical procedure will be used to control the risk of concluding erroneously.	• Anti-PRP antibody concentrations at 1-month post-booster vaccination. • Anti-PRP antibody concentration ≥5 µg/mL at 1-month post-booster vaccination.
Secondary	
Descriptive To assess the immunogenicity of Hib-components in terms of percentage of subjects above the thresholds for short-term (≥0.15 µg/mL) and long-term (≥1.0 µg/mL) protection as well as in terms of GMCs (post-primary, pre- and post-booster vaccination)	Anti-PRP antibody concentrations at 1-month post-primary vaccination, pre-booster and 1-month post-booster vaccination.
To assess the safety of *Infanrix hexa* and *Vaxelis* co-administered with *Prevenar 13*™ in terms of unsolicited adverse events (AEs) and serious adverse events (SAEs)	• Occurrence of unsolicited AEs during the 31 day (Days 1-31) follow-up period after each vaccination. • Occurrence of SAEs after first dose up to study end.

Objectives	Endpoints
Tertiary	
CCI [redacted]	

The tertiary objective may be reported separately.

Overall Design:

This is a phase IV, single-blind, randomised, controlled and multi-country study with 2 parallel groups of healthy infants and toddlers aged 6 to 12 weeks at the time of first vaccination.

Treatment allocation: The subjects will be randomised at a 1:1 ratio to Inv_group or Com_group using a minimisation algorithm with the study country and maternal immunisation of the infants as minimisation factors. This will be done at the study entry using an Interactive Voice Response System (IVRS) randomisation.

Number of Investigators and Study Centres:

Approximately 35 investigators and study centres in about 3 European countries are expected to participate in this study.

Number of Subjects:

The study will enrol 500 subjects in a 1:1 ratio. Assuming that 20% of the subjects would not be evaluable, the power was computed for 400 evaluable subjects (i.e., 200 subjects each in the Inv_group and Com_group). For more information, see Section 9.0, Statistical Considerations, and Section 9.2, Sample Size Determination.

Treatment Groups and Duration:

There will be 2 parallel groups of subjects:

- Inv_group (Investigational group): All subjects in this group will receive 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of *Prevenar 13* at 2, 4, and 12 months.
- Com_group (Comparator group): All subjects in this group will receive 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of *Prevenar 13* at 2, 4, and 12 months.

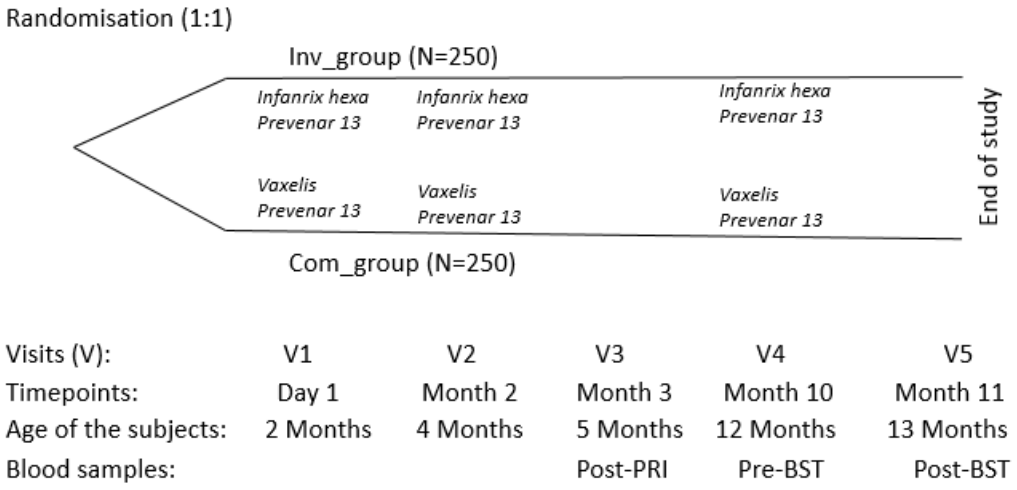
Duration of the study: The intended duration of the study per subject is approximately 11 months, divided into 2 study phases.

- Study phase 1: Primary study phase, starting at Visit 1 (Day 1) and ending at Visit 3 (Month 3); i.e., 1 month following the second primary dose.
- Study phase 2: Booster study phase, starting at Visit 4 (Month 10) and ending at Visit 5 (Month 11); i.e., 1 month after the booster dose.

Data Monitoring Committee: No.

1.2 Schema

Figure 1 Study Schema



BST=booster, PRI=primary

1.3 Schedule of Activities

Table 3 Schedule of Activities

Age	**2 Months**	**4 Months**	**5 Months**	**12 Months**	**13 Months**
Study phase	**Study phase 1 (Primary)**			**Study phase 2 (Booster)**	
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Sampling time points			**Post-primary**	**Pre-booster**	**Post-booster**
Informed consent by parents/LAR(s)	●				
Check inclusion/exclusion criteria	●				
Check contraindications to vaccination	○	○		○	
Collect demographic data (including gestational age)	●				
Vaccination history and maternal dTpa immunisation	●				
Vaccines					
Study group and treatment number allocation	○				
Treatment number allocation for subsequent doses		○		○	
Recording of administered treatment number	●	●		●	
Vaccine administration	●	●		●	
Clinical specimens for laboratory assays					
Blood sampling for antibody determination (~2.5 mL)			●	●	●

Age	**2 Months**	**4 Months**	**5 Months**	**12 Months**	**13 Months**
Study phase	**Study phase 01 (Primary)**			**Study phase 02 (Booster)**	
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Sampling time points			**Post-primary**	**Pre-booster**	**Post-booster**
Safety assessments					
Medical history	●				
Check contraindications, warnings and precautions to vaccination	○	●		●	
Pre-vaccination body temperature[a]	●	●		●	
Record any concomitant medication/vaccination	●	●	●	●	●
Distribution of memory aids	○	○		○	
Return of memory aids		○	○		○
Recording of unsolicited AEs[b] (including the review of memory aids)	●	●	●	●	●
Reporting of SAEs[c]	●	●	●	●	●
Study Conclusion					●

AEs=adverse events; SAEs=serious adverse events; dTpa=combined reduced-antigen-content diphtheria, tetanus and acellular pertussis; LAR=legally acceptable representative.

[a] Fever is defined as temperature ≥38°C (regardless of route). Rectal temperature is preferred, but oral or axillary temperature is also allowed.

[b] AEs collected during 31-day follow-up period after each vaccination.

[c] SAEs collected throughout study.

● = study procedure that requires documentation in the individual eCRF.

○ = study procedure that does not require documentation in the individual eCRF.

2.0 INTRODUCTION

Infanrix hexa was registered in Europe in 2000 and is currently licensed for primary and booster vaccination in more than 90 countries worldwide. Since launch more than 186 million doses of *Infanrix hexa* have been distributed worldwide. *Infanrix hexa* has a well-characterised safety profile and has a large cumulative post-marketing exposure suggesting the benefit/risk profile continues to be favourable.

2.1 Study Rationale

Aside from *Infanrix hexa*, 2 other hexavalent combination vaccines are currently available: *Hexyon/Hexacima/Hexaxim*™ (registered by Sanofi Pasteur in 2013) and *Vaxelis*™ (registered by MCM Vaccine BV in 2016). The *Haemophilus influenzae* type b (Hib) component of *Infanrix hexa* is lyophilised, and it must be reconstituted with the sterile suspension containing the other vaccine antigens prior to its administration, while *Hexyon/Hexacima/Hexaxim* and *Vaxelis* are fully liquid vaccines.

Available data from the clinical development of *Vaxelis* show that following the primary vaccination in infants, *Vaxelis* (containing a Hib-outer membrane protein [Hib-OMP] which is covalently bound to polyribosylribitol phosphate [PRP]) shows a higher anti-PRP antibody response than *Infanrix hexa* (PRP conjugated to tetanus toxoid [TT] carrier protein [Hib-TT]). However, the observed anti-PRP geometric mean concentrations (GMCs) following *Vaxelis* booster dose in toddlers was lower as compared to *Infanrix hexa*, [EMA, 2016; Vesikari, 2017; Silfverdal, 2016].

In Europe, there is evidence of successful Hib disease control with *Infanrix hexa* 3+1 and 2+1 schedules, which also includes data between 2005 and 2013 when *Infanrix hexa* was the only hexavalent vaccine available in Europe [Wang, 2017]. The lower anti-PRP antibody response post-booster vaccination with *Vaxelis* could lead to rapid waning of immunity or have a negative effect on the Hib carriage/transmission rates in the population [EMA, 2016]. It is known that the presence of circulating anti-PRP antibodies at sufficient concentrations at the time of exposure to Hib is critical to prevent invasive disease [Barbour, 1996]. Therefore, the difference in the booster responses between the 2 vaccines may have significant implications on Hib disease control and public health.

The co-primary objectives of this study are (1) to demonstrate non-inferiority of *Infanrix hexa* versus *Vaxelis* in terms of anti-PRP GMCs and proportion of subjects with antibody concentrations equal to or above 5 µg/mL following the booster dose in a 2+1 schedule (2-, 4-, and 12-month); (2) to demonstrate superiority of *Infanrix hexa* versus *Vaxelis* in terms of anti-PRP GMCs and proportion of subjects with antibody concentrations above 5 µg/mL following the booster dose in a 2+1 schedule (2-, 4-, and 12-month). The potential differences in anti-PRP antibody avidity for the 2 vaccines may also be explored in this study.

2.2 Background

Barbour et al. report that the acquisition of Hib or the prolonged Hib carriage in the nasopharynx may occur only below a threshold concentration of serum or mucosal anti-PRP antibodies [Barbour, 1996]. Other literature reports that high anti-PRP antibody concentrations above the established correlates of clinical protection (0.15 µg/mL for short-term and 1.0 µg/mL for long-term protection) may be needed to reduce Hib nasopharyngeal colonisation and carriage [Peltola, 1977; Käyhty, 1983]. Also, the protection against colonisation seems to be well correlated with anti-PRP antibody concentrations ≥5 µg/mL at 1 month following the third vaccine dose in infants [Fernandez, 2000]. Comparative data on the proportion of subjects reaching the 5 µg/mL titre after *Infanrix hexa* or *Vaxelis* are not publicly available. In addition, little is known about antibody quality [Agbarakwe, 1995, Schlesinger, 1992].

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of *Infanrix hexa, Vaxelis*, and *Prevenar 13*™ are provided in the current Summaries of Product Characteristics (SmPCs).

2.3 Benefit/Risk Assessment

Subjects' parents or legally acceptable respresentative(s) (LARs) will be informed of the benefits and risks of participation in the study before they consent to the subjects' participation.

The benefit of vaccination in infants and toddlers includes protection from multiple diseases which have high morbidity and mortality rates. Both *Infanrix hexa* and *Vaxelis* are designed to prevent diphtheria, tetanus, pertussis, hepatitis B virus (HBV), polio, and diseases caused by Hib, and vaccination against these 6 diseases is recommended by the national health authorities in Europe.

Risks may include injection site reactions, fever, hypersensitivity to vaccine ingredients and/or excipients.

As applicable for all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of *Infanrix hexa, Vaxelis*, and *Prevenar 13* may be found in their respective SmPCs.

3.0 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are presented in Table 4.

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Co-primary	
Confirmatory 1.To demonstrate that the Hib response in Investigational group (Inv_group) is non-inferior to Comparatory group (Com_group), 1-month post-booster vaccination in terms of: • GMCs o *Criterion: Lower limit (LL) of the 2-sided 95% confidence interval (CI) on group GMC ratio (Inv_group over Com_group) is above 0.5.* • Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL. o *Criterion: First primary objective is met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is more than -10%.* 2.To demonstrate that the Hib response in Inv_group is superior to Com_group, 1-month post-booster vaccination in terms of: • GMCs o *Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group GMC ratio (Inv_group over Com_group) is above 1.* • Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL. o *Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above 0.* • Note: A hierarchical procedure will be used to control the risk of concluding erroneously.	• Anti-PRP antibody concentrations at 1-month post-booster vaccination. • Anti-PRP antibody concentration ≥5 µg/mL at 1-month post-booster vaccination.

Objectives	**Endpoints**
Secondary	
Descriptive To assess the immunogenicity of Hib-components in terms of percentage of subjects above the thresholds for short-term (≥0.15 µg/mL) and long-term (≥1.0 µg/mL) protection as well as in terms of GMCs (post-primary, pre- and post-booster vaccination).	Anti-PRP antibody concentrations at 1-month post-primary vaccination, pre-booster and 1-month post-booster vaccination.
To assess the safety of *Infanrix hexa* and *Vaxelis* co-administered with *Prevenar 13* in terms of unsolicited adverse events (AEs) and serious adverse events (SAEs).	• Occurrence of unsolicited AEs during the 31 day (Days 1-31) follow-up period after each vaccination. • Occurrence of SAEs after first dose up to study end.
Tertiary/Exploratory	
CCI [redacted]	

The tertiary objective may be reported separately.

4.0 STUDY DESIGN

4.1 Overall Design

This is a phase IV, single-blind, randomised, controlled and multi-country study in infants and toddlers 6 to 12 weeks of age at the time of first vaccination.

The subjects will be assigned to 1 of 2 parallel groups:

- Inv_group (Investigational group): All subjects in this group will receive 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of *Prevenar 13* at 2, 4, and 12 months.
- Com_group (Comparator group): All subjects in this group will receive 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of *Prevenar 13* at 2, 4, and 12 months.

Duration of the study: The intended duration of the study per subject is approximately 11 months, divided into 2 study phases.

- Study phase 1: Primary study phase, starting at Visit 1 (Day 1) and ending at Visit 3 (Month 3), i.e., 1 month following the second primary dose.
- Study phase 2: Booster study phase, starting at Visit 4 (Month 10) and ending at Visit 5 (Month 11), i.e., 1 month after the booster dose.

Treatment allocation: The subjects will be randomised at a 1:1 ratio to Inv_group or Com_group using a minimisation algorithm with the study country and maternal immunisation status as minimisation factors. This will be done at study entry using an Interactive Voice Response System (IVRS) randomisation.

Proposed countries: About 3 European countries.

Sampling schedule: Blood samples will be collected from all subjects at the following time points:

- Post-Primary (Visit 3): At 1 month after the second dose of primary vaccination, a volume of approximately 2.5 mL of whole blood will be collected.
- Pre-Booster (Visit 4): Before the administration of the booster dose, a volume of approximately 2.5 mL of whole blood will be collected.
- Post-Booster (Visit 5): At 1 month after the booster vaccination, a volume of approximately 2.5 mL of whole blood will be collected.

Data collection: electronic Case Report Form (eCRF).

4.2 Scientific Rationale for Study Design

This study is designed to have 2 parallel groups to have a head-to-head comparison of Hib immune responses for *Infanrix hexa* versus *Vaxelis* as:

- data from a literature review show differences in the Hib immune response between *Infanrix hexa* and *Vaxelis* post-primary and post-booster vaccination, and
- this difference is seen both in fold change of anti-PRP antibody concentrations and in anti-PRP GMCs [EMA, 2016; Vesikari, 2017; Silfverdal, 2016].
- It is also known that the presence of circulating anti-PRP antibodies at sufficient concentrations at the time of exposure to Hib is critical to prevent invasive disease [Barbour, 1996].

Therefore, the difference in the booster responses between the 2 vaccines may have significant implications on Hib disease control and public health.

Prevenar 13 is co-administered with both *Infanrix hexa* and *Vaxelis* in this study as vaccination with a pneumococcal conjugate vaccine is part of the national recommendations in Europe.

This head-to-head study of *Infanrix hexa* versus *Vaxelis* is proposed to address:

- the evidence gaps regarding the proportion of subjects ≥5 µg/mL anti-PRP antibody threshold, and,
- the uncertainties regarding the quality of the anti-PRP antibodies generated by both vaccines.

4.3 Justification for Dose

For this study, a 2+1 vaccination schedule (2-, 4- and 12-month) has been selected, as several European countries are either adopting and/or have implemented this schedule already in their national immunisation schedules [ECDC, 2019].

4.4 End of Study Definition

A subject is considered to have completed the study if he/she returns for the last visit as described in the protocol.

End of study (EoS) is defined as the release date of the last testing results of samples collected at Visit 5.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

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

Subjects are eligible to be included in the study only if ALL of the following criteria apply at study entry.

1. Subjects' parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., return for follow-up visits)
2. Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
3. A male or female child between and including 6 and 12 weeks of age (42 to 84 days) at the time of the first vaccination.
4. Subject born after at least 37 weeks of gestation.
5. Healthy subjects as established by the investigator based on medical history and the clinical examination before entering into the study.

5.2 Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise 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 is met, the subject must not be included in the study.

5.2.1 Medical Conditions

1. Any clinical condition that, in the opinion of the investigator, might pose any risk to the subject due to participation in the study. As with other vaccines, administration of *Infanrix hexa* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contraindication.
2. Known history of diphtheria, tetanus, pertussis, HBV, poliomyelitis and Hib diseases since birth.
3. History of any reaction or hypersensitivity likely to be caused or exacerbated by any excipient or active component of the vaccine(s).

4. Any confirmed or suspected immunosuppressive or immunodeficient condition, including malignancies, based on medical history and physical examination (no laboratory testing required).
5. Family history of congenital or hereditary immunodeficiency.
6. Major congenital defects, as assessed by the investigator.
7. Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined via medical history including physical examination.
8. Medical history of neurological disorder, including seizures.

5.2.2 Prior/Concomitant Therapy

9. Previous vaccination for diphtheria, tetanus, pertussis, HBV, poliomyelitis, Hib diseases and previous vaccination against pneumococcal infection with pneumococcal conjugate vaccine, with the exception of a birth dose of HBV vaccine, which may be given in accordance with local recommendations.
10. Use of any investigational or nonregistered product (drug, vaccine, or medical device) other than the study vaccine(s) during the period starting 30 days before the first dose of study vaccine(s) (Day -29 to Day 1), or planned use during the study period.
11. Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of vaccine(s) with the exception of administration of vaccines given as part of the national immunisation schedule and as part of routine vaccination practice, e.g., rotavirus vaccine, that are allowed at any time during the study period. In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organised by public health authorities outside the routine immunisation programme, the time period described above can be reduced if necessary for that mass vaccination vaccine, provided this vaccine/product(s) is licensed and used according to its Product Information.
12. Administration of long-acting immune-modifying drugs in the period starting 30 days before the first dose and at any time during the study period.
13. Administration of immunoglobulins and/or any blood products or plasma derivatives from birth or planned administration during the study period.
14. Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.

5.2.3 Prior/Concurrent Clinical Study Experience

15. 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 (drug or medical device).

5.2.4 Other Exclusions

16. Child in care.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as subjects whose parent(s) or LAR(s) give consent for the subject to participate in the clinical study, but are not subsequently entered in the study. Screen failure information is maintained by the investigator as source data.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol. Study treatments administered are presented in Table 5.

6.1 Study Treatment(s) Administered

Table 5 Treatments Administered

Study Treatment	***Infanrix hexa***		***Vaxelis***	***Prevenar 13***
Vaccine/ Product	**DTPa-HBV-IPV**	**Hib**	***Vaxelis***	***Prevenar 13***
Presentation	Suspension for injection, Syringe	Powder for suspension for injection, Vial	Suspension for injection, Syringe	Suspension for injection, Syringe
Number of Doses	3		3	3
Dose Volume	~0.5 mL[a]		0.5 mL	0.5 mL
Route of Administration	IM injection, right thigh		IM injection, right thigh	IM injection, left thigh
Dosing Instructions	Refer to and follow the SmPC or directions for handling and administration.		Refer to and follow the SmPC or directions for handling and administration.	Refer to and follow the SmPC or directions for handling and administration.
Packaging and Labelling	Study treatment will be provided in a carton, containing 1 vial and 1 prefilled syringe without needles. Each carton will be clinically labeled as required per country requirement.		Study treatment will be provided in a carton, 1 prefilled syringe without needles. Each carton will be clinically labeled as required per country requirement.	Study treatment will be provided in a carton, 1 prefilled syringe without needles. Each carton will be clinically labeled as required per country requirement.
Manufacturer	GSK Biologicals		MCM Vaccine BV	Pfizer
QA Release for Study	GSK Biologicals		GSK Biologicals	GSK Biologicals

Study Treatment	***Infanrix hexa***		***Vaxelis***	***Prevenar 13***
Vaccine/ Product	**DTPa-HBV-IPV**	**Hib**	***Vaxelis***	***Prevenar 13***
Dosage Formulation	Diphtheria toxoid (≥30 I.U.) adsorbed on aluminium hydroxide; Tetanus toxoid (≥40 I.U.) adsorbed on aluminium hydroxide; *Bordetella pertussis* antigens-Pertussis toxoid (PT) (25 µg) adsorbed on aluminium hydroxide; *Bordetella pertussis* antigens-Filamentous Haemagglutinin (FHA) (25 µg) adsorbed on aluminium hydroxide; *Bordetella pertussis* antigens-Pertactin (PRN) (8 µg) adsorbed on aluminium hydroxide; Hepatitis B surface antigen (HBs) (10 µg) adsorbed on aluminium phosphate; Poliovirus (inactivated) (IPV) type 1 (Mahoney strain) (40 DAgU); Poliovirus (inactivated) (IPV) type 2 (MEF-1 strain) (8 DAgU); Poliovirus (inactivated) (IPV) type 3 (Saukett strain) (32 DAgU); Aluminium hydroxide ($Al(OH)_3$)/Aluminium phosphate ($AlPO_4$) (0.7 mg Al^{3+}); Medium 199; Sodium chloride; Water for injections q.s. 0.5 mL	*Haemophilus influenzae* type b polysaccharide (polyribo-sylribitol phosphate, PRP) (10 µg) conjugated to tetanus toxoid (~25 µg) adsorbed on aluminium phosphate; Aluminium phosphate; Lactose	Diphtheria toxoid (not less than 20 I.U.) adsorbed on aluminium phosphate; Tetanus toxoid (not less than 40 µg I.U.) adsorbed on aluminium phosphate; *Bordetella pertussis* antigens - Pertussis toxin (20 µg) adsorbed on aluminium phosphate; *Bordetella pertussis* antigens - Filamentous haemagglutinin (20 µg) adsorbed on aluminium phosphate; *Bordetella pertussis* antigens - Pertactin (3 µg) adsorbed on aluminium phosphate; *Bordetella pertussis* antigens - Fimbriae type 2 and 3 (5 µg) adsorbed on aluminium phosphate; Hepatitis B surface antigen (10 µg) adsorbed on amorphous aluminium hydroxyphosphate sulfate; Poliovirus (Inactivated) Type 1 (Mahoney) (40 D antigen units); Poliovirus (Inactivated) Type 2 (MEF-1) (8 D antigen units); Poliovirus (Inactivated) Type 3 (Saukett) (32 D antigen units); *Haemophilus influenzae* type b polysaccharide (Polyribosylribitol Phosphate) (3 µg) conjugated to meningococcal protein (50 µg) adsorbed on amorphous aluminium hydroxyphosphate sulfate; Aluminium phosphate (0.17 mg Al^{3+}); Amorphous aluminium hydroxyphosphate sulfate (0.15 mg Al^{3+}); Glutaraldehyde (Traces); Formaldehyde (Traces); Neomycin (Traces); Streptomycin (Traces); Polymyxin B (Traces); Sodium phosphate; Water for injections q.s. 0.5 mL	Pneumococcal polysaccharide serotype 1 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 3 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 4 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 5 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 6A (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 6B (4.4 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 7F (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 9V (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 14 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 18C (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 19A (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 19F (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 23F (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Total CRM_{197} carrier protein (32 µg [EU]/34 µg [US]); Aluminium phosphate (0.125 mg Al^{3+}); Sodium chloride; Succinic acid; Polysorbate 80; Water for injections q.s. 0.5 mL

Subjects must be observed closely for at least 30 minutes after the administration of the vaccines. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.

Infanrix hexa and *Vaxelis* are administered IM to the right thigh; *Prevenar 13* is administered to the left thigh.

Abbreviations: IPV=inactivated poliovirus vaccine.

a. Full volume after reconstitution (approximately 0.5 mL) to be administered.

6.2 Contraindications to Subsequent Vaccination

6.2.1 Criteria for Temporary Delay of Vaccination

Vaccination may be delayed temporarily in the case of acute disease and/or fever at the time of vaccination.

- Fever is defined as temperature ≥38.0°C.
- Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

In case of fever at the time of vaccination, the vaccination visit could be rescheduled, within the time window specified in [Table 8].

6.2.2 Other Contraindications to Subsequent Vaccination

For additional information regarding contraindications to subsequent vaccination, refer to the respective SmPCs for *Infanrix hexa*, *Vaxelis*, and *Prevenar 13*.

6.2.3 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 subject should remain under medical supervision for 30 minutes after vaccination.

6.3 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorised study centre staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised study centre staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the site study reference manual.

The investigator, a member of the study centre staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

To maintain blinding, vaccination doses will be prepared in a separate room, out of sight of subjects/LARs.

6.4 Measures to Minimise Bias: Randomisation and Blinding

6.4.1 Subject Identification

After checking the inclusion and exclusion criteria, 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 the/each study centre.

6.4.2 Randomisation to Study Intervention

All eligible subjects will be centrally randomised using IVRS randomisation. Before the study is initiated, log-in information and directions for the IVRS will be provided to each site. As this is a randomised single-blind study, the study treatment assigned to the subject will be known by the investigator, but the subject will be blinded to the treatment received.

Once a treatment number has been assigned it cannot be re-assigned.

6.4.3 Intervention Allocation to the Subject

Treatment allocation: The subjects will be randomised in a 1:1 ratio to either the Inv_group or Com_group (Section 1.2 and Section 6.1) using a minimisation algorithm with the study country and maternal immunisation as minimisation factors. This will be done at study entry, i.e., on Day 1 after consent was obtained and subjects were determined to be eligible, using IVRS randomisation.

6.4.4 Allocation Treatment Number for Subsequent Dose or Replacement

For all subsequent doses, new treatment numbers will be obtained through the IVRS.

6.4.5 Blinding and Unblinding

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted and subject treatment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. A subject may continue in the study if that subject's intervention assignment is unblinded.

Unblinded monitors and, in the event of a Quality Assurance audit, the auditor(s), will be allowed access to unblinded study treatment information records at the site(s) to verify that randomisation/dispensing has been done accurately.

Despite the fact that this is a single-blind study, the data management and biostatistics teams will remain blinded to the study treatment until after the final database lock. No unblinded data summaries (presented by treatment) will be available prior to the final database lock. An independent unblinded Biostatistician will be identified to review potentially unblinding information ahead of the final database lock, e.g., randomisation specifications and schedule.

6.5 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs. For dosing instructions and route, refer to Table 5.

6.6 Concomitant Therapy

Exclusionary concomitant therapies are described in exclusion criteria Section 5.2.2.

At each trial visit/contact, the investigator or delegate should question the participant's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the participant. The following concomitant medications/products/vaccines must be recorded in the eCRF:

- ***All concomitant medications/products associated with an AE, except vitamins and dietary supplements, administered following each dose of investigational vaccine (Day 1 to Day 31).***
- ***Any vaccination administered in the period from birth until 30 days after the last dose of study vaccines.***
- ***Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination or blood sampling), for example:***
  - ***An antipyretic 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 [100.4°F] regardless of the location of measurement).***
  - ***A topical local anesthetic used prior to a blood sampling is considered to be prophylactic.***
- ***Any concomitant medications/products/vaccines listed in Section 5.2.2.***

• Any concomitant medications/products/vaccines relevant to an SAE or administered at any time during the trial period for the treatment of an SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the Expedited AE Report.

These medication***s/products/***vaccine***s*** must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Prophylactic administration of antipyretics (paracetamol/acetaminophen and ibuprofen) before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions.

If the subject has a history of febrile seizures, prophylactic antipyretic treatment should be initiated according to local treatment guidelines.

(Section 6.6 amended 06 April 2021)

6.7 Dose Modification

This protocol does not allow alteration from the currently outlined dosing schedule.

6.8 Treatment After the End of the Study

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

For subjects identified as non-responders, it is the responsibility of the investigator in charge of the subject's clinical management to determine the medical care needed as per local/regional practices (such as re-vaccination of the subject[s]).

- Immunological correlate of protection: Data from subjects given unconjugated Hib vaccine suggest that, in the absence of induction of immunological memory, a concentration of 0.15 µg/mL is indicative of short-term protection, with 1 µg/mL considered indicative of long-term protection [Anderson, 1984; Käyhty, 1983].

During the study conclusion visit, the investigator will ask each subject's parent(s)/LAR(s) if they are interested in participating in a potential study to evaluate the persistence of the Hib immune response. If they are not interested in participating in such a study the reason for refusal will be documented, when available, in the subject's eCRF.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Discontinuation of study vaccine(s) means any subject who has not received all planned doses of vaccine(s). A subject who discontinued study vaccine(s) may, if deemed appropriate by the investigator, continue other study procedures (e.g., safety or immunogenicity) if planned in the study protocol.

7.2 Subject Discontinuation/Withdrawal from the Study

- Parents or LARs may withdraw a subject from the study at any time on request, or a subject may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.
- If the subject's parents or LARs withdraw consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject is withdrawn from the study, the subject's parents or LARs may request destruction of any samples taken and not tested, and the investigator must document this in the study centre study records.

Subjects who discontinue study treatment or are withdrawn will not be replaced. The eCRF should be completed as much as possible.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if his or her parents or LARs fail to return the subject for scheduled visits and are unable to be contacted by the study centre.

The following actions must be taken if a subject's parents or LARs fail to return him or her to the clinic for a required study visit:

- The study centre must attempt to contact the parents/LARs and reschedule the missed visit as soon as possible, and counsel the parents/LARs on the importance of maintaining the assigned visit schedule and ascertain whether or not the parents/LARs wish the subject to continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the parents or LARs (where possible, 3 telephone calls and, if necessary, a certified letter to the parents'/LAR's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the parents or LARs continue to be unreachable, the subject will be considered to have withdrawn from the study.

7.4 Reason for Discontinuation

Subjects may be withdrawn from the treatment and the study for any of the following reasons:

- The parents or LARs withdraw consent on behalf of the subject.
- The parents or LARs are unwilling or unable to comply with the protocol.
- Adverse event(s).
- Lost to follow-up.
- Protocol deviation(s).
- Occurrence of contraindications that were not present at enrolment.
- If, in the clinical judgment of the investigator, it is not in the subject's best interest to continue with the study treatment.

The reason for the subject's withdrawal from the study or from treatment must be recorded in the subject's eCRF. When a subject is withdrawn, the date of last contact and reason for treatment/study withdrawal (see above) should be clearly described in the relevant sections of the eCRF. If a subject is removed from study or treatment because of an AE, the reason for treatment withdrawal should always be stated as "adverse event" irrespective of whether this was the investigator's or the parents' or LARs' decision. The subject should be followed until the event has resolved, stabilised, or returned to baseline.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the Schedule of Activities (SoA) [Table 3].
- Protocol waivers or exemptions are not allowed unless necessary for the management of an immediate safety concerns.
- Immediate safety concerns should be discussed with the Sponsor upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, as specified in the SoA, is essential and required for study conduct.
- The investigator is not allowed to do testing on samples outside of what has been agreed upon by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- An overall blood volume of 7.5 mL will be collected during the entire study period. Refer to the SoA for details of volumes collected for different assessments as presented in Table 6 (laboratory assays).

8.1 Immunogenicity Assessments

Blood samples of approximately 2.5 mL each will be obtained at Visit 3, Visit 4 and Visit 5 [Table 6]. Please refer to the Laboratory Manual for details on biospecimen management (handling, storage and shipment). Tests will be conducted at the Sponsor's laboratory, or laboratories designated by the Sponsor. All blood sample testing is based on in-house assays. GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

Refer to Table 6 for the laboratory assays to be performed and the SoA [Table 3] for the timing and frequency. See Table 10 for addresses of the clinical laboratories used for sample analysis.

Collected biological 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.

Future findings may make it desirable to use the samples acquired in this study for future research not described in this protocol, such as immunogenicity testing of the other study vaccines' antigens. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to prior IEC/IRB approval if required per local legislation.

- Collected samples will be stored for a maximum of 20 years. This storage period begins when the last subject performs the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with subject consent. These extra requirements need to be communicated formally to, and discussed and agreed on with, GSK.

Table 6 Laboratory Assays

Sampling Time Points	System	Component	Method	Unit	Number of Subjects
	Humoral immunity				
Month 3, Month 10, and Month 11	Serum	anti-PRP antibody	ELISA[a]	µg/mL	All

CCI [redacted]

CCI [redacted] ELISA=enzyme linked immunosorbent assay

CCI [redacted]

8.2 Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE [Appendix 4]. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the subject to discontinue the study intervention or discontinue from study.

8.2.1 Physical Examinations

- A brief history-directed physical examination will include, at a minimum, assessment of body temperature and vital signs.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Subject vaccination history and maternal dTpa immunisation history will be collected.

8.2.2 Vital Signs

Temperature will be taken before each vaccination (i.e., at Visit 1, Visit 2 and Visit 4). Rectal temperature is preferred, but oral or axillary temperature is also allowed. Fever is defined as ≥38˚C, regardless of route.

If the subject has a fever, the vaccination should be postponed and a new visit scheduled considering the allowed visit windows.

8.3 Adverse Events

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from Visit 1 through study end, at the time points specified in the SoA [Table 3].

All AEs will be collected from vaccination through the 31-day follow-up period after each vaccination, as specified in the SoA [Table 3].

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Memory aids used by subjects' parent(s)/LAR(s) will be reviewed for health related issues of subjects and for potential AEs which will be transcribed in eCRFs. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject's parents or LARs is the preferred method to inquire about AE occurrences.

For any unplanned/routine laboratory investigation performed, the investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the AE Section of the CRF/eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All clinically significant abnormal laboratory test values during the study or within 31 days after the last dose of study intervention should be repeated until the values return to normal or baseline, or are no longer considered significantly abnormal by the investigator or LML. Refer to Appendix 4 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.

- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met. For SAEs, the investigator will always provide an assessment of causality at the time of the initial report, as defined in the Appendix 4.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Subject Card

The investigator (or designee) must provide the subjects' parent(s)/LAR(s) with a "subject card" containing information about the clinical study. The subject's parent(s)/LAR(s) must be instructed to keep the subject card in his/her/their possession at all times throughout the study. In an emergency, this card serves to inform the responsible attending physician/LAR/care giver/family member that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

8.4 Treatment of Overdose

Not applicable.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

For the co-primary endpoints, a hierarchical procedure will be used to control the risk of concluding erroneously.

To demonstrate that the Hib response in Inv_group is non-inferior to Com_group, 1-month post-booster vaccination in terms of:

- GMCs
    - Criterion: Lower limit (LL) of the 2-sided 95% confidence interval (CI) on group GMC ratio (Inv_group over Com_group) is above 0.5.
- Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL.
    - Criterion: First primary objective is met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above -10%.

To demonstrate that the Hib response in Inv_group is superior to Com_group, 1-month post-booster vaccination in terms of:

- GMCs
    - Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group GMC ratio (Inv_group over Com_group) is above 1.
- Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL.
    - Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above 0.

9.2 Sample Size Determination

The study will enrol approximately 500 subjects in a 1:1 ratio. Assuming that 20% of the subjects would not be evaluable, the power was computed for 400 evaluable subjects (i.e., 200 subjects each in the Inv_group and Com_group). Evaluable is defined as: meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, qualified for inclusion in the according-to-protocol analysis.

A 2.5% nominal type I error was used for each co-primary evaluation. To control the overall type I error below 2.5%, a hierarchical procedure will be used for the multiple study objectives. The study has:

- More than 99% power to reach the first co-primary objective. This power is obtained from PASS 2012, 1-sided t-test (non-inferiority with 0.5 group ratio as margin, i.e., -0.301 in $\log_{10}$ Scale) for 2 independent means with common 0.63 variance of $\log_{10}$ transformed anti-PRP concentration, under the specific alternative that the group GMC ratio is 1.75 [Silfverdal, 2016], i.e., 0.2430 in $\log_{10}$ scale, and
- More than 99% power to reach the second co-primary objective. This power is obtained from PASS 2012, 1-sided Miettinen and Nurminen [Miettinen, 1985] test (non-inferiority with -10% margin) for 2 independent proportions under the specific alternative that the proportions are 46% after *Vaxelis* and 62% after *Infanrix hexa* [Silfverdal, 2016] while accounting for the power to meet the first co-primary objective.
- Approximately 97% power to reach the third co-primary objective. This power is obtained from PASS 2012, 1-sided t-test (inequality) for 2 independent means with common 0.63 variance in $\log_{10}$ scale, under the specific alternative that the group GMC ratio is 1.75 [Silfverdal, 2016], i.e., 0.2430 in $\log_{10}$ scale while accounting for the power to meet the first co-primary objective.
- At least 80% power to reach all co-primary objectives. This power is obtained from PASS 2012, 1-sided Z test (inequality) with pooled variance for 2 independent proportions under the specific alternative that the proportions are 46% after *Vaxelis* and 62% after *Infanrix hexa* [Silfverdal, 2016] while accounting for the power to meet the first 3 co-primary objectives.

9.3 Analysis Sets

For purposes of analysis, the analysis sets are defined in Table 7.

Table 7 Analysis Sets

Analysis Set	Description
Enrolled set	All subjects with a study intervention (either randomised or vaccinated or with a blood draw).
Exposed set (ES)	All vaccinated subjects. Subjects will be analysed according to the intervention they received at Dose 1.
Per protocol set (PPS)	All eligible subjects who received all DTPa-combination study vaccines as per protocol, who had anti-PRP results post-vaccination, who complied with vaccination/blood draw intervals (Table 8), without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Subjects will be analysed according to the intervention they received at Dose 1.

Table 8 Intervals Between Study Visits

Interval	Length of interval	Allowed interval
Birth (age is 0 day on birth date)→ Visit 1	6 to 12 weeks	42 to 84 days
Visit 1 → Visit 2	60 days	52, 78 days
Visit 2 → Visit 3	30 days	21, 48 days
Birth → Visit 4	365 days	335, 395 days
Visit 4 → Visit 5	30 days	21, 48 days

9.4 Statistical Analyses

The Statistical Analysis Plan will be developed and finalised before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All analyses, summaries, and listings will be performed using SAS® software (version 9.4 or higher).

Individual subject data will be presented in listings.

9.4.1 Disposition

The number of subjects screened, randomised, treated and who completed the study will be presented. For subjects who discontinue the treatment/study, the reason for discontinuing early will also be presented.

9.4.2 Demographics and Other Baseline Characteristics

Baseline and demographic information will be summarised using descriptive statistics for continuous and ordinal variables (e.g., age, weight, height [Day 1 only]) and counts and percentages for categorical variables (e.g., sex, race).

9.4.3 Immunogenicity Analyses

The confirmatory analyses of non-inferiority will be based on the PPS while the confirmatory analyses of superiority will be based on the ES.

- Method for non-inferiority and superiority in anti-PRP antibody concentration at 1-month post-booster vaccination:

- The 2-sided 95% CI for group GMC ratio derived from an ANOVA model on log_{10} transformed concentration will be used. The model will include country, maternal immunisation and group as fixed effects. (Missing data will not be replaced. Concentration below assay cut-off will be replaced by half the assay cut-off).

- Method for non-inferiority and superiority in the percentage of subjects with anti-PRP antibody concentration ≥5.0 µg/mL at 1-month post-booster vaccination:
  - The 2-sided 95% CI on group difference in seroconversion rate (Inv_group minus Com_group) will be computed based on Miettinen and Nurminen method [Miettinen, 1985].
- Descriptive analysis for each study group will be provided by country for Anti-PRP antibody concentrations at 1-month post-primary vaccination, pre-booster and 1-month post-booster vaccination, and for the percentage of subjects with anti-PRP antibody concentration ≥5.0 µg/mL at 1-month post-booster vaccination.

9.4.4 Safety Analyses

Descriptive analyses for the AEs and SAEs will be provided by study group. Safety data will be analysed on the ES population.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, numbers of AEs and percentage of subjects with AE within 31 days post-vaccination will be tabulated by preferred term and system organ class.

9.4.5 Sequence of analyses

An integrated clinical study report containing all data will be written and made available to the investigators. The data for tertiary objectives may be reported in an annex report if not available at the time the integrated clinical study report is prepared

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes.

9.4.6 Interim Analyses

No interim analysis for efficacy is planned.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations and Glossary of Terms

AE:	Adverse Event
CI:	Confidence Interval
Com_group:	Comparator group
dTpa:	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis vaccine
DTPa-HBV-IPV/Hib	Diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and *Haemophilus influenzae* type b conjugate vaccine
eCRF:	electronic Case Report Form
EoS	End of Study
ES:	Exposed Set
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GSK:	GlaxoSmithKline Biologicals SA
HBV	Hepatitis B virus
Hib:	*Haemophilus influenzae* type b
Hib-OMP:	Hib component of *Vaxelis;* outer membrane protein (OMP) that is covalent bound to polyribosylribitol phosphate (PRP)
Hib-TT:	PRP conjugated to tetanus toxoid (TT) carrier protein
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
Inv_group:	Investigational group
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LAR:	Legally acceptable representative
LL:	Lower limit
µg	Microgram
mL	Millilitre
PPS:	Per Protocol Set
PRP:	Polyribosylribitol phosphate

SAE:	Serious Adverse Event
SoA	Schedule of Activities
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

Glossary of Terms

Adverse event:	Any untoward medical occurrence in a subject 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 a single-blind study, the investigator knows the identity of the treatment assigned while the subject's parent(s)/legally acceptable representatives(s) don't know.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study: (Synonym of End of Trial)	For studies without collection of human biologicals samples or imaging data End of Study (EoS) is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV
Study phase:	A study phase is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints

	within that study phase allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of study phases are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the Per Protocol Set (PPS).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Intercurrent medical condition:	A condition that has the capability of altering a subject's immune response or are confirmed to have an immunodeficiency condition during the study.
Investigational vaccine: (Synonym of Investigational Medicinal Product)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Legally Acceptable Representative (LAR) (The terms legal representative or legally authorised representative are used in some settings.)	An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
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.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
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 number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.

Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccines or as a control.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
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.

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

Companies/organisations responsible for conducting the study are presented in Table 9.

- This study will be conducted in accordance with the protocol and with the following:

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
Applicable laws.

- The protocol, protocol amendments, Informed Consent Form (ICF), SmPCs, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the study centre and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 6). The study will not start at any study centre at which the investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject subject's parents or LARs and answer all questions regarding the study.
- The subject's parents or LARs must be informed that participation is voluntary. The subject's parents or LARs will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's LAR.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Administrative Structure

Table 9 Study Administrative Structure

Function	Responsible Organisation
Study Operations Management Medical Monitoring, Study Master File	IQVIA
Randomisation Code	Cenduit
Clinical Supply Management, Quality Assurance Auditing	GSK
Biostatistics Medical Writing	IQVIA
Laboratory Assessments	GSK
Electrocardiogram Collection, Review, and Analysis	Not applicable
Pharmacokinetic Sample Testing	Not applicable

Medical Monitor

Refer to study reference manual.

Dissemination of Clinical Study Data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study register in compliance with the applicable regulations/GSK policy. GSK will aim to register protocol summaries prior to study start and target result summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with study subjects, as appropriate.

GSK will provide the investigator with randomisation codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymised subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical

science or improve subject care. This helps ensure the data provided by trial subjects are used to maximum effect in the creation of knowledge and understanding.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised study centre personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study centre's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's study centre.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for

the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

- Source documents are defined as original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aids or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Study and Study Centre Closure

The Sponsor designee reserves the right to close the study centre or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centres will be closed upon study completion. A study centre is considered closed when all required documents and study supplies have been collected and a study centre closure visit has been performed.

The investigator may initiate study centre closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study centre by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further study treatment development.

Publication Policy

GSK aims to submit for publication the results of the study in searchable, peer reviewed scientific literature within 18 months from Last Subject Last Visit (LSLV) for interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

Appendix 3 Clinical Laboratory Tests

- The immunogenicity tests detailed in Table 6 will be performed.

All laboratory testing will be performed at GSK's laboratory or in a laboratory designated by GSK. All blood sample testing is based on in-house assays.

Laboratory/analyte results that could unblind the study will not be reported to study centres or other blinded personnel until the study has been unblinded.

Table 10 GSK Biologicals' Laboratories

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

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: 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 study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • 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 study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, or that present or are detected at the start of the study and do not worsen. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • 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.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

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 inpatient hospitalisation or prolongation of existing hospitalisation

In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or an outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered as serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

d) Results in persistent disability/incapacity

- 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, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include 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.

If an event meets the criteria to be determined as "serious", 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).

Assessment of Outcome

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).

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to IQVIA in lieu of appropriate completion of the IQVIA/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by IQVIA. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to IQVIA.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study vaccine(s) and the occurrence of each AE/SAE using clinical judgment. In case of concomitant administration of multiple vaccines, if possible, the Investigator should specify if the AE could be causally related to a specific vaccine administered (i.e., investigational or co-administered vaccine). When causal relationship to a specific vaccine(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(s) will be considered and investigated. The Investigator will also consult the SmPC and/or Prescribing Information (PI) for marketed products to determine his/her assessment.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report to IQVIA. 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 IQVIA. 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.

Causality of all unsolicited 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 study vaccine?

YES: There is a reasonable possibility that the study vaccine(s) contributed to the AE.

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

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the SmPC and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to IQVIA. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to IQVIA.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator will provide any new or updated relevant information on previously reported SAE to GSK using a paper/electronic Expedited Adverse Events Report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

Reporting of SAEs

SAE Reporting to IQVIA via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to IQVIA will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the study centre will use the paper SAE data collection tool (see next section). • The study centre will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given study centre, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a study centre receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study centre can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in the study reference manual.

Back-up SAE Reporting to IQVIA via Paper (in Case of Electronic System Failure)
• Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE eCRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the study reference manual.

Appendix 5 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Protocol Amendment 1 (additions **bold** and *italic*; deletions strikethrough ~~and~~):

Synopsis and Section 3.0: Addition of "≥" to the secondary immunogenicity objective, preceding the numbers of the thresholds for short-term and long-term protection:

To assess the immunogenicity of Hib-components in terms of percentage of subjects above the thresholds for short-term (≥0.15 µg/mL) and long-term (≥1.0 µg/mL) protection as well as in terms of GMCs (post primary, pre- and post-booster vaccination).

Section 6.6:

Exclusionary concomitant therapies are described in exclusion criteria Section 5.2.2.

At each trial visit/contact, the investigator or delegate should question the participant's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the participant. The following concomitant medications/products/vaccines must be recorded in the eCRF:

- ***All concomitant medications/products associated with an AE, except vitamins and dietary supplements, administered following each dose of investigational vaccine (Day 1 to Day 31).***
- ***Any vaccination administered in the period from birth until 30 days after the last dose of study vaccines.***
- ***Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination or blood sampling), for example:***
  - ***An antipyretic 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 [100.4°F] regardless of the location of measurement).***
  - ***A topical local anesthetic used prior to a blood sampling is considered to be prophylactic.***
- ***Any concomitant medications/products/vaccines listed in Section 5.2.2.***
- ***Any concomitant medications/products/vaccines relevant to an SAE or administered at any time during the trial period for the treatment of an SAE. In addition,***

concomitant medications relevant to SAEs need to be recorded on the Expedited AE Report.

These ~~Concomitant medications/vaccinations information will be collected at each study visit.~~ medication***s/products***/~~or~~ vaccine***s*** ~~(including over-the-counter or prescription medicines) that the subject is receiving at the time of enrolment (or within 14 to 30 days before the time of enrolment, as detailed in Section 5.2.2) or receives during the study~~ must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

~~A list of excluded medications/therapy is provided in Section 5.2.2.~~

Prophylactic administration of antipyretics (paracetamol/acetaminophen and ibuprofen) before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions.

Appendix 6 Signature of Investigator

PROTOCOL TITLE: A phase IV, single-blind, randomised, controlled, multi-country study to evaluate the immunogenicity and safety of GSK's *Infanrix hexa* (DTPa-HBV-IPV/Hib) versus MCM Vaccine BV's *Vaxelis* (DTaP5-HBV-IPV-Hib), when administered intramuscularly according to a 2-, 4- and 12-month schedule in healthy infants and toddlers

PROTOCOL NO: 212645

VERSION: Amendment 1

This protocol is a confidential communication of GlaxoSmithKline Biological SA. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study centre in which the study will be conducted. Return the signed copy to IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Centre: _____

_____

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