STATISTICAL ANALYSIS PLAN

Protocol 212645

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.

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 07JAN2021) for Protocol 212645.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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1.0	07Jan2021	PPD	Not Applicable – First Version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AI	Avidity index
ANOVA	Analysis of variance
ATC	Anatomical therapeutic chemical
BST	Booster
CI	Confidence Interval
Com_group	Comparator group
CSR	Clinical Study Report
DMC	Data Monitoring committee
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
ENR	Enrolled Set
ES	Exposed Set
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus
Hib	*Haemophilus influenzae* type b
ICH	International Council on Harmonisation
Inv_group	Investigational group
LL	Lower limit
LLOQ	Lower limit of quantitation

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
NI	Non-inferiority
PD	Protocol deviation
PDMP	Protocol deviation management plan
PRI	Primary
PRP	Polyribosylribitol phosphate
PT	Preferred term
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
UL	Upper limit
ULOQ	Upper limit of quantification
V	Visit

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and immunogenicity data at final analyses for Protocol 212645. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on the original Protocol Version 1 dated 21 Feb 2020.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The co-primary objectives are:

- To demonstrate that the Hib response in Investigational group (Inv_group) is non-inferior to the Comparator group (Com_group), 1-month post-booster vaccination in terms of:
  - Geometric Mean Concentration (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.
- Note: A hierarchical procedure will be used to control the risk of concluding erroneously.

2.2. SECONDARY OBJECTIVES

The secondary objectives are :

- 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).
- 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).

2.3. TERTIARY/EXPLORATORY OBJECTIVES

The exploratory/tertiary objective is:

CCI [redacted]

- The tertiary objective may be reported separately.

2.4. ENDPOINTS

Table A: List of Endpoints

Objectives	Endpoints	Definition	Analysis set
Co-primary	Non-inferiority: Anti-PRP antibody concentration ≥5µg/mL at 1-month post-booster vaccination	• 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 at 1-month post booster vaccination o Criterion: First primary objective is met	Per protocol set (PPS)

		and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above -10%.	
	Superiority: Anti-PRP antibody concentration ≥5µg/mL at 1-month post-booster vaccination	• 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.	Exposed Set (ES)
Secondary	Anti-PRP antibody concentrations at 1-month post-primary vaccination, pre-booster and 1-month post-booster vaccination.	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)	ES & PPS
	Occurrence of unsolicited AEs during the 31-day (Days 1-31) follow-up period after each vaccination.	Percentage of subjects with any unsolicited AEs (including all SAEs) during the 31-day (Days 1-31) follow-up period after each vaccination	ES
	Occurrence of SAEs after first dose up to study end.	Percentage of subjects with SAEs throughout the study period.	ES
Tertiary/Exploratory	CCI [redacted]		ES & PPS

		CCI [redacted]	

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

Approximately 500 subjects will be randomised/vaccinated in a 1:1 ratio. They will be randomised to 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.

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.

For more information, see Section 4.0 of the Protocol.

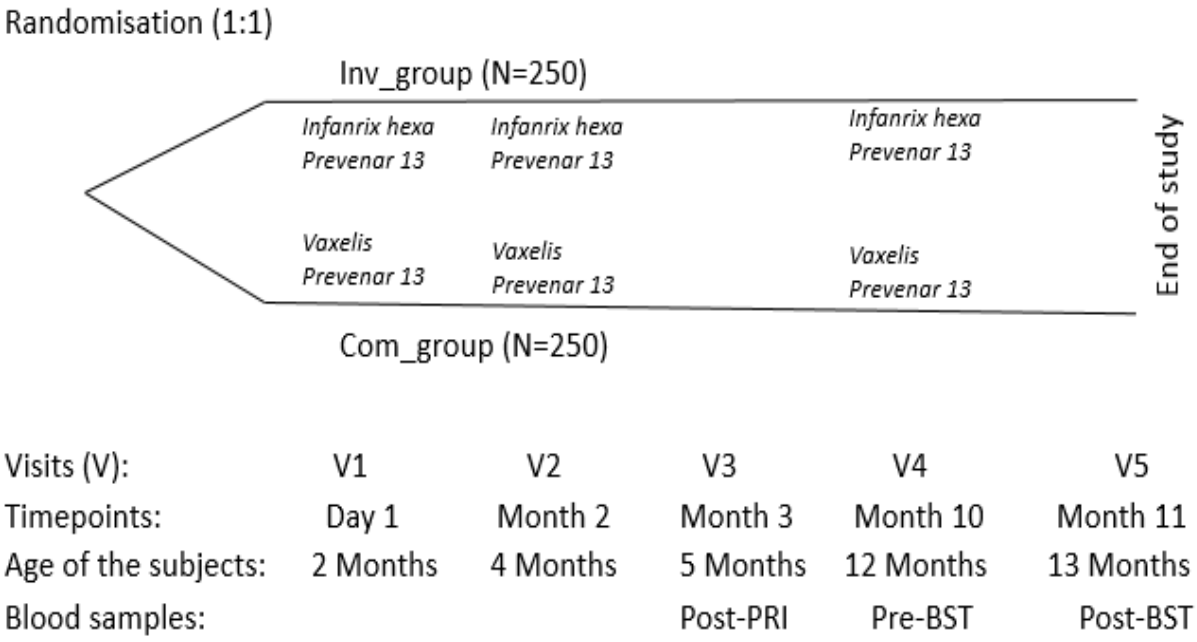
Table B: Treatment Group, Treatment and Dosing

Study Phase	Type of Contact and Timepoint	Treatment Group	Treatment Name	# of Doses	Age of subjects
Phase 1 (Primary)	Visit 1 Day 1	Inv_group (Investigational group)	Infanrix hexa	1 (PRI)	2 months
			Prevenar 13™	1 (PRI)	
		Com_group	Vaxelis	1 (PRI)	

		(comparator group)	Prevenar 13™	1 (PRI)	
Phase 1 (Primary)	Visit 2 Month 2	Inv_group (Investigational group)	Infanrix hexa	1 (PRI)	4 months
			Prevenar 13™	1 (PRI)	
		Com_group (comparator group)	Vaxelis	1 (PRI)	
			Prevenar 13™	1 (PRI)	
Phase 2 (Booster)	Visit 4 Month 10	Inv_group (Investigational group)	Infanrix hexa	1 (BST)	12 months
			Prevenar 13™	1 (BST)	
		Com_group (comparator group)	Vaxelis	1 (BST)	
			Prevenar 13™	1 (BST)	

PRI=primary, BST=booster

Figure A: Study Schema



BST=booster, PRI=primary

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the Protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Given the current climate with COVID-19 pandemic, additional analyses for subjects diagnosed with COVID-19 will be performed. This will be assessed on a case by case basis (e.g., adapted missing data imputation techniques, subgroup analyses to explore the indirect or direct impact of COVID-19) and discussed in an SAP addendum as needed.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC planned for this study.

4.2. INTERIM ANALYSIS

There will be no interim analysis planned for this study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following GlaxoSmithKline Biologicals SA authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Intervention.

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. PROCESS FOR ANALYSIS SET ASSIGNMENT

- Definitions for analysis sets are provided below.
- Prior to database lock, a transfer of raw data from the eCRF will occur, and subjects will be assigned to analysis sets in accordance with the definitions in this SAP and the available data at that time. However, the protocol deviations will be monitored continuously throughout the study.
- Listings presenting subjects excluded from each preliminary analysis set and reasons for exclusion will be prepared for sponsor review ahead of database lock in order to allow appropriate related data

queries to be issued.

- Listings presenting subjects excluded from each final analysis set and reasons for exclusion will be prepared for sponsor review ahead of unblinding for a final review and approval. However, for deviations that can only be assessed after unblinding (such as vaccination errors or pre and post booster samples), these will be reviewed after unblinding.
- A Data Review meeting will be held to confirm analysis set assignment for each subject and any changes will be recorded. Changes will be implemented, and an updated analysis set assignment will be approved by the sponsor.
- Sponsor authorization of the analysis sets will be necessary to unblind the data after database lock. Once approved, analysis sets will be finalized, and the database will be locked.
- After database lock, the final analysis sets will be derived using the final study data, i.e., clinical database (CRF), external vendor data (immunogenicity results) and protocol deviations log.

5.2. ENROLLED SET [ENR]

The enrolled set (ENR) will include all subjects with a study intervention (either randomised or vaccinated or with a blood draw).

5.3. EXPOSED SET [ES]

The exposed set (ES) will include all vaccinated subjects with ICF and exclude any fraudulent data. Subjects will be analysed according to the intervention they received at Dose 1.

5.4. PER PROTOCOL SET [PPS]

The per protocol set (PPS) will include all eligible subjects from the exposed set who received all study vaccines as per protocol, who had anti-PRP results post-vaccination, who complied with vaccination/blood draw intervals, 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. Refer to Section 6.2 for details on the intervals.

More specifically, the analysis at 1 month post-booster vaccination based on the PPS will include all eligible subjects:

- who received all the study vaccines up to booster dose as per the vaccination schedule and for whom administration route of study vaccines up to booster dose was as per protocol;
- who did not receive a medication/product before the blood sampling at Visit 4 (Month 10) which led to elimination from PPS;
- who did not present with a contraindication before the blood sampling at Visit 4 (Month 10) which led to elimination from PPS;
- who complied with the post-booster blood sample schedule, i.e. 21-48 days post-booster vaccination;
- who were not administered a vaccine not foreseen by the study protocol before the corresponding post-vaccination blood sample collection;
- who had immunogenicity results at 1-month post-booster vaccination;

Likewise, the analysis at 1 month post-dose 2 based on the PPS will include all eligible subjects:

- who received all the study vaccines up to second dose as per the vaccination schedule and for whom administration route of study vaccines up to second dose was as per protocol;
- who did not receive a medication/product before the blood sampling at Visit 3 (Month 5) which led to elimination from PPS;
- who did not present with a contraindication before the blood sampling at Visit 3 (Month 5) which led to elimination from PPS;
- who complied with the post-primary blood sample schedule, i.e. 21-48 days post-dose 2 vaccination;
- who were not administered a vaccine not foreseen by the study protocol before the corresponding post-dose 2 vaccination blood sample collection;
- who had immunogenicity results at 1-month post-dose 2 vaccination;

6. GENERAL CONSIDERATIONS

Data will be summarised descriptively (frequency and percentage for categorical data and mean and standard deviation [SD] for continuous data, unless specified otherwise). In summary tables for categorical data for which categories are defined on the electronic case report form (eCRF), all categories will be presented as specified, even if the subject count within that category is zero.

Unless otherwise specified, all data collected during the trial will be presented in listings.

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.
Reference start date is defined as the day of the first dose of study treatment, (Day 1 is the day of the first dose of study treatment).

- If the date of the event is on or after the reference date, then:
  Study Day = (date of event – reference start date) + 1.

- If the date of the event is prior to the reference date, then:
  Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings. Refer to Appendix 2 for partial date conventions.

6.2. WINDOWING CONVENTIONS

The following table describes assignment of visit windows for two reasons:

- Vaccination and blood draw intervals for purposes of analysis.
- If a subject has fever (temperature >= 38°C), the vaccination should be postponed, and a new visit will be scheduled.

Table C: 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 to 78 days
Visit 2 → Visit 3	30 days	21 to 48 days
Birth → Visit 4	365 days	335 to 395 days
Visit 4 → Visit 5	30 days	21 to 48 days

Interval is computed as the difference between the 2 dates meaning that visit 2 should be on or between Day 53 and Day 79. In other words, a subject with dose 2 vaccination on January 1 will be eliminated if the blood draw is on January 21 but will not be eliminated if the blood draw is on January 22.

6.3. STATISTICAL TESTS

The default confidence interval level will be 2 sided 95% with equal tail, unless otherwise specified in the description of the analyses.

6.4. COMMON CALCULATIONS

Geometric Mean Concentration (GMC)

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers or concentrations will be log10-transformed. GMCs and their 95% CIs are computed by exponentiating (base 10) the least squares mean and 95% CIs of the log10 titers.

The GMC will be calculated using the following formula:

$$10^{\left(\frac{\sum_{i=1}^{n}\log 10(t_i)}{n}\right)}$$

Where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers/concentrations.

Concentration below assay cut-off (i.e., <lower limit of quantitation or < LLOQ) will be replaced by half the assay cut-off (LLOQ/2) for the purpose of GMC computation.

6.5. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following factors will be used in the analyses. For details, refer to Section 16.1 and 16.2. The model will include country, maternal immunisation and treatment group as fixed categorical effects in the Analysis of Variance (ANOVA) model.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centres in 3 European countries. 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.

Descriptive immunogenicity analysis will be performed by country (refer to section 7.5). Country will be pooled for safety and inferential analysis. Additional analyses by country will be conducted as deemed necessary as per Section 7.5.

7.3. MISSING DATA

Missing data (missing, incomplete or partial dates, AE measurement (including missing AE severity and relationship), prior and concomitant medications and death date) will be handled as per Appendix 2 of this analysis plan.

Missing immunogenicity data will not be imputed. Concentration below assay cut-off (i.e., lower limit of quantitation or < LLOQ) will be replaced by half the assay cut-off (LLOQ/2) for the purpose of GMC computation.

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CCI

[redacted]

7.4. ACTIVE-CONTROL STUDIES INTENDED TO SHOW NON-INFERIORITY OR SUPERIORITY

Non-inferiority will be demonstrated in terms of an endpoint if:

- 1. The lower limit of 2-sided 95% confidence interval (CI) on group GMC ratio (Inv_group over Com_group) from the ANOVA model is above 0.5.
- 2. The lower limit of the 2-sided 95% CI on group difference in the percentage (inv_group minus Com_group) is above -10%.

Superiority will be demonstrated in terms of an endpoint if:

- 3. The lower limit of 2-sided 95% confidence interval (CI) on group GMC ratio (Inv_group over Com_group) from the ANOVA model is above 1.
- 4. The lower limit of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above 0.

For each objective, concluding is only possible if the previous objective(s) (ie 1, 2, 3 as shown above) in the hierarchy has been reached
Additional details provided in Section 16.1.

7.5. EXAMINATION OF SUBGROUPS

Descriptive summaries of immunogenicity analyses will be performed by country and by maternal immunization status, respectively unless a subgroup covers less than 50 subjects in the PPS at one month post booster dose or more than the total number of subjects in the PPS minus 50 at one month post booster dose.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.
The templates that will be provided with this SAP describe the presentations for this study and therefore the format

and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics. Statistical output numbering will follow 'ICH E3 Structure and Content of Clinical Study Reports'.

9. DISPOSITION AND WITHDRAWALS

All subjects who are enrolled in the study (those with a study intervention either randomised or vaccinated or with a blood draw) will be accounted for in this study.

9.1. DISPOSITION

Subject disposition, withdrawals, and reasons for exclusion from each analysis set, including inclusion as well as exclusion criteria will be presented for the ENR set. Specifically, the number of subjects, treated and completed the study will be summarized by study arm for the ENR set. Additionally, the number of subjects returning for each visit, discontinuing treatment but who continued further study procedures, discontinuing the study and the reason for discontinuation will be presented.

A listing of the disposition for all subjects with early withdrawal or discontinuation due to having COVID-19 or COVID-19 related issues information will be provided.

9.2. PROTOCOL DEVIATIONS

- Protocol deviations (PDs) will be collected in a PD log, as detailed in the Protocol Deviations Management Plan (PDMP).
- All PDs will be assessed as important and non-important. Protocol deviations will be reviewed by the sponsor, and their status confirmed by the time that all data are cleaned for the Final Analysis.
- A summary table presenting the frequency and percentage of subjects with important PDs will be presented for subjects in the ENR set.
- A listing of all PDs including an indicator of those excluded from the PPS and an indicator of COVID causality will be provided.

9.2.1. PROTOCOL DEVIATIONS RELATED TO STUDY CONDUCT

A PD is any noncompliance with the clinical trial protocol, good clinical practice (GCP), or Manual of Procedure

requirements. The noncompliance may be either on the part of the subject, the site PI, the study site staff or the sponsor.

9.2.2. PROTOCOL DEVIATIONS RELATED TO IMMUNOGENICITY ANALYSIS

Changes to the procedures or events, which may impact the quality of the immunogenicity data, will be considered significant PDs and will be described within the clinical study report (CSR). This includes any circumstances that could alter the evaluation of the immunogenicity results such as sample processing errors that lead to inaccurate immunogenicity results, and/or inaccurate dosing which could exclude them from the PPS. In addition, subjects may also be eliminated from the PPS based on usage of certain concomitant medications or vaccines as described in Section 5.2.2 of the original Protocol version 1 dated 21 Feb 2020.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ENR, ES and PPS analysis sets.
The following demographic and other baseline characteristics will be reported for this study:

- Age (weeks) – at the time of first vaccination
- Gestational age (weeks)
- Sex
- Race (as per CDISC categories)
- Country
- Weight (kg)
- Height (cm) at Day 1
- Maternal immunisation status

Descriptive statistics (mean, median and standard deviation) will be presented for continuous variables and frequency counts and percentages for categorical variables. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DERIVATIONS

- Age (weeks) at first vaccination = int ((Date of first vaccination – Date of birth + 1) / 7)
- Partial dates will be handled as per the rules in Appendix 2.

11. COVID -19 CORONAVIRUS INFECTION ASSESSMENT AND DIAGNOSIS

The COVID-19 infection assessment and diagnosis data including assessment, symptom, level of care and diagnosis data will be presented for the ES and captured on the "COVID-19 Coronavirus Infection Assessment and Diagnosis" page of the eCRF.

A listing of this data will be provided.

12. GENERAL MEDICAL HISTORY AND EXAMINATIONS

Medical History and Examination information will be presented for the ENR.

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 23.0 or higher.
- Data captured on the "General Medical History" page of the eCRF will be presented by SOC (System Organ Class) and PT (Preferred Term). 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.

In addition, if a medical disorder, allergy or surgery may be relevant to a SAE (Serious Adverse Event), this information will be recorded under the "Relevant Medical Condition(s)/ Risk Factor(s)" section of the "Expedited Adverse Events" page of the eCRF.

A listing of medical history data will be provided.

13. PRIOR, CONCOMITANT AND CO-ADMINISTERED VACCINATIONS

Prior, concomitant and co-administered vaccination will be coded with the GSK drug dictionary summarized by ingredient for the ES.

- Prior vaccinations are vaccinations given to subjects prior to the first dose of study treatment and are recorded on the eCRF.

- *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.
- Concomitant vaccinations are defined as any vaccine that the subject is receiving as of the time of enrolment or receives during the study, other than study vaccine(s) as recorded on the "Concomitant Vaccination" page of the eCRF.

Co-administered vaccinations will be summarized for each dose while prior/concomitant vaccinations will be summarized by period:

- Before Dose 1
- Between Dose 1 & Dose 2 (this will include the concomitant vaccinations which took place after dose 1 when dose 2 was not given)
- Between Dose 2 & Visit 3 (this will include the concomitant vaccinations which took place between Dose 2 & booster dose when visit 3 is missing; this will include the concomitant vaccinations which took place after Dose 2 for subject who dropped out between Dose 2 and Visit 3)
- Between Visit 3 and booster dose (this will include the concomitant vaccinations which took place after visit 3 for subject who dropped out between Visit 3 and booster dose).
- After booster dose

Further details are in Section 5.2.2 of the Protocol.

In addition, if a concomitant vaccination may help explain an AE/SAE, the cause of the AE/SAE or the treatment of an AE/SAE, this information will be recorded under the "Relevant Concomitant/Treatment Medications/Vaccinations Entry" section of the "Expedited Adverse Events" page of the eCRF.

Data will be presented in tables summaries and listings.

14. MEDICATIONS

The percentage of subjects who started medications after Dose 1 will be presented by treatment group for the ES. The percentage of subjects who started medications with antipyretic action for any reason and for prophylactic reason will also be summarized. The antipyretic action will be derived from the anatomical therapeutic chemical (ATC) coding as per the latest version of the GSK drug dictionary.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a

medication as prior or after dose 1, the medication will be classified by the worst case; i.e. after dose 1.

- 'Prior' medications are medications which started prior to the first dose of study treatment.
- 'Concomitant' medications are any other medications which are received during the study as recorded on the "Medication" page of the eCRF (ended on or after the date of first dose of study medication or were ongoing at the end of the study)

Further details are in Section 5.2.2 of the Protocol.

15. STUDY TREATMENT EXPOSURE AND COMPLIANCE

Study treatment exposure will be presented for the ES. The distribution of the total number of *Infanrix hexa/ Vaxelis* doses will be summarized for the ES. The prescribed dosage, timing, and mode of administration may not be changed with any departures from the intended regimen recorded on the "Study Vaccine / Product Administration" page of the eCRF. For dosing instructions and route, refer to Table 3 on page 24 of the original Protocol version 1 dated 21 Feb 2020.

Compliance to study treatment will be presented for the ES. The frequency and percentage of subjects receiving 1 dose, 2 doses or all 3 doses will be presented overall and by treatment group.

Data will be presented in tables summaries and listings.

16. IMMUNOGENICITY OUTCOMES

16.1. PRIMARY IMMUNOGENICITY

16.1.1. PRIMARY IMMUNOGENICITY VARIABLE(S) & DERIVATION(S)

The primary immunogenicity objective to demonstrate that the Hib response in the investigational group is non-inferior to the Comparator group at 1-month post-booster vaccination will be based on the PPS. The primary immunogenicity objective to demonstrate that the Hib response in the investigational group is superior to the Comparator group at 1-month post-booster vaccination will be based on the ES.

16.1.2. Missing Data Methods for Primary Immunogenicity Variable(s)

Missing data will not be replaced. Refer to Section 7.3.

16.1.3. Primary Analysis of Primary Immunogenicity Variable(s)

In order to assess non-inferiority and superiority, the associated co-primary endpoints are assessed:

- anti-PRP antibody concentrations at 1-month post-booster vaccination
- anti-PRP antibody concentrations ≥5.0 µg/mL at 1-month post-booster vaccination

They are assessed in terms of:

- An adjusted GMC and GMC ratio with 2-sided 95% CI for treatment group which is derived from an ANOVA model on log10 transformed concentration will be tabulated for anti-PRP antibody concentrations. The model will include country, maternal immunisation and group as fixed effects. The Lower limit (LL) of the 2-sided 95% confidence interval (CI) on group GMC ratio (Inv_group over Com_group) will be calculated by exponentiating (base10) the least squares means and the lower and upper limits of the 95% CIs of the log transformed titers (base10) obtained from an ANOVA with factors for vaccine group, maternal immunisation and country.
- Percentage of subjects with anti-PRP antibody concentration ≥5.0 µg/mL at 1-month post-booster vaccination using 2-sided 95% CI on group difference in the percentage/seroconversion rate (Inv_group minus Com_group) computed based on Miettinen and Nurminen method [Miettinen, 1985].

Refer to Section 2.1 for the criteria used to make conclusions.

16.2. Secondary Immunogenicity

The analyses will be based on the PPS and ES.

16.2.1. Secondary Immunogenicity Variables & Derivations

In order 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):

- Descriptive analysis for each treatment group will be provided by country and maternal immunisation for anti-PRP antibody concentrations at 1-month post-primary vaccination, pre-booster and 1-month post-booster vaccination for the PPS and ES. This analysis will also be provided per subgroup for the PPS as per Section 7.5.
- GMC and its associated 2-sided 95% CI will be calculated on all subjects by treatment groups at 1-month post-primary, pre-booster and 1-month post-booster vaccination.
- The number and percentage of subjects with anti-PRP antibody concentrations ≥0.15 µg/mL, ≥1.0 µg/mL, ≥5.0 µg/mL at 1-month post-primary, pre-booster and 1-month post-booster vaccination with associated 2-sided 95% CI will be provided by treatment groups. Clopper and Pearson exact CI will be used for proportions.
- An adjusted GMC and GMC ratio with 2-sided 95% CI for treatment group which is derived from an ANOVA model on log10 transformed concentration will be tabulated for anti-PRP antibody concentrations. The model will include country, maternal immunisation and group as fixed effects.
- Reverse cumulative curves at each time point will also be displayed by treatment group for the ES and PPS.

16.2.2. Missing Data Methods for Secondary Immunogenicity Variable(s)

Missing data will not be replaced. Refer to Section 7.3.

16.3. Tertiary Immunogenicity

CCI

CCI

[redacted]

CCI

[redacted]

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the ES.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 23.0 or higher.

Partial dates will be handled based on information available in Appendix 2

17.1.1. UNSOLICITED AES, INCLUDING SAES

For each study treatment, the incidence rates (frequencies and percentages) of subjects/events with unsolicited AEs, including serious AE, occurring within 31-days (Days 1-31) follow-up period after any dose will be presented by System Organ Class (SOC) and Preferred Term (PT) with 95% Clopper Pearson exact CI. Similar tabulation will be done for unsolicited AEs rated by maximum severity, for unsolicited AEs with causal relationship to vaccination as defined by the investigator.

17.1.1.1. Assessment of Intensity

Severity is classified as mild/ moderate/ severe (increasing severity) AEs starting after the first dose of study treatment with a missing severity will not be accounted in the analysis of "Severe" AEs. If a subject report an AE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

17.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classified as "Yes" if causally related to "Hexavalent vaccine" or "*Prevenar 13*".

17.1.2. SERIOUS AEs

For each study treatment, the incidence rates (frequencies and percentages) of subjects with SAE occurring after the first study dose will be presented by System Organ Class (SOC) and Preferred Term (PT) with 95% Clopper Pearson exact CI. Similar tabulation will be done for SAE with causal relationship to vaccination as defined by the investigator; for fatal SAE and for causally related fatal SAE. Serious AEs will be recorded on the "Expedited Adverse Events" page of the eCRF.

17.1.3. UNSOLICITED AE, EXCLUDING SAEs

For each study treatment, the incidence rates (frequencies and percentages) of subjects with unsolicited AEs, excluding serious AE, occurring within 31-days (Days 1-31) follow-up period after any dose will be presented by System Organ Class (SOC) and Preferred Term (PT) without 95% Clopper Pearson exact CI. The number of events defined as the number of PT with different start date will be included in the summary. This summary is needed for web posting and will not be part of the study report. Unsolicited AEs excluding SAEs will be recorded on the "Non-Serious Adverse Events and Intercurrent Medical Conditions" pages of the eCRF.

Listings of AEs and SAEs leading to withdrawal of study treatment and AEs and SAEs leading to death will be provided.

17.2. VITAL SIGNS AND PHYSICAL EXAMINATION

The following vital sign measurements collected at Day 1 will be reported for this study:

- Weight (kg)
- Height (cm)

A listing of this data will be provided. Descriptive statistics of the vital signs will be presented along with demographic characteristics.

18. REFERENCES

Clopper CJ, Pearson ES. The use of confidential or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26:404-413

Miettinen O., Nurminen M. Comparative analysis of 2 rates. Statistics in Medicine 1985; 4(2):213-26

Nauta J. Statistics in Clinical Vaccine Trials. 2010. Heidelberg: Springer.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following IQVIA Output Conventions

Document Headers
All TFL is to include the following header:

GSK Vaccines Vaccine: *Infanrix hexa* Study 212645 (DTPa-HBV-IPV-141) - *DELIVERY DESIGNATION*

where delivery designation is the name of the current delivery, e.g., DRY-RUN, FINAL ANALYSIS REPORT, etc

DATES

Depending on data available, dates will take the form yyyy-mmm-dd.

ATTRIBUTING EVENTS TO VACCINE DOSES

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1. If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the relative dose for the event will be the dose prior to this one.

ONSET DAY

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

SPELLING FORMAT

English UK.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Vaccine Group	**For Table, Listings and Figures**
Infanrix hexa	*Infanrix hexa*
Vaxelis	*Vaxelis*
Prevenar 13	*Prevenar 13*

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Visit 1	V1
Visit 2	V2
Visit 3	V3
Visit 4	V4
Visit 5	V5

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Vaccine group (or intervention received if it's a safety output),
- Center-subject ID,
- Date (where applicable),

- Subjects without Hexavalent vaccine administered will appear in a treatment groups labeled 'Not vaccinated with Hexavalent vaccine.' in listings.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the data listings.

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

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

The following exceptions apply:

- Adverse event start dates with missing day:

  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.

- Adverse event start dates with missing day and month:

  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

Approved By:	PPD	Refer to eSignature
Position:	Lead Scientific Writer	
Company:	GlaxoSmithKline Biologicals SA	

PPD

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	03 Feb 2021 22:15:46 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	08 Feb 2021 05:50:36 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	01 Apr 2021 09:34:15 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	01 Apr 2021 11:22:20 UTC