| | |
|---|---|
| GlaxoSmithKline | **Statistical Analysis Plan** |
| **Detailed Title:** | A phase IV, open-label, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a challenge dose of hepatitis B vaccine (Engerix-B™ Kinder SKF103860) in children aged 14-15 years, previously primed and boosted in the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix™ hexa SB217744) vaccine |
| **eTrack study number and Abbreviated Title** | 106794 (DTPA-HBV-IPV-115) |
| **Scope:** | All data pertaining to the above study. |
| **Date of Statistical Analysis Plan** | 01-Aug-2017 |
| **Co-ordinating authors:** | PPD (Statistician) PPD (Statistician) |
| **Reviewed by:** | PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead Statistician – Combination Vaccines) PPD (Lead Statistical analyst) PPD (Scientific writer) PPD (Lead Scientific writer) PPD (Global Regulatory Affairs) PPD (SERM physician) PPD (Public disclosure representative) PPD (Stat Peer reviewer) |
| **Approved by:** | PPD (Clinical and Epidemiology Project Lead) PPD (Lead Statistician – Combination Vaccines) PPD (Lead Scientific writer) PPD (Lead Statistical analyst) |

***APP 9000058193 Statistical Analysis Plan Template ( Effective date: 14 April 2017)***

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## LIST OF TEMPLATES

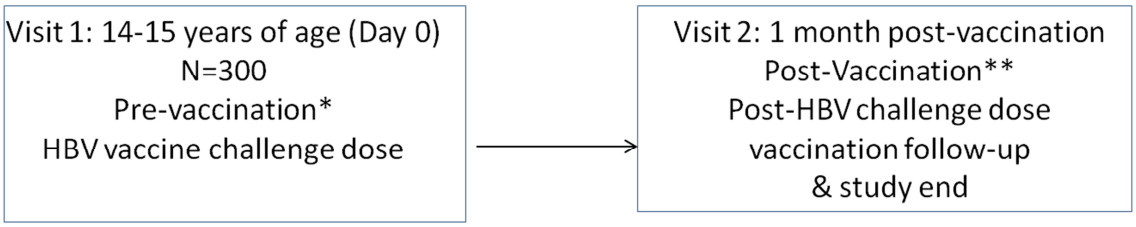
## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CTRS | Clinical Trial Registry Summary |
| GMC | Geometric mean antibody concentration |
| GSK | GlaxoSmithKline |
| LL | Lower Limit of the confidence interval |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mIU/ml | Milli-International units per milliliter |
| NA | Not Applicable |
| PD | Protocol Deviation |
| RCC | Reverse Cumulative Curve |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SR | Clinical Study Report |
| SR | Study Report |
| TFL | Tables Figures and Listings |
| TOC | Table of Content |
| UL | Upper Limit of the confidence interval |

# 1. DOCUMENT HISTORY

| Date | Description | Protocol Version |
|---|---|---|
| 01-AUG-2017 | Final Version | Final - 06 November 2015 |

# 2. STUDY DESIGN




N: Number of subjects planned to be enrolled
* Pre-vaccination: Blood sampling before the administration of the single HBV vaccine challenge dose
** Post-vaccination: Blood sampling one month after the administration of the single HBV vaccine challenge dose

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

- Experimental design: Phase IV, open-label, non-randomised, multi-centric, single-country study with a single group.
- Duration of the study: the intended duration of the study, per subject, will be approximately one month. The study will have a single epoch as follows:
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 2 (Month 1).
- Study groups: the details are presented below in Table 1.

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

| Study groups | Number of subjects | Age (Min/Max) | Epochs |
|---|---|---|---|
| | | | Epoch 001 |
| HBV Group | 300 | 14 years – 15 years | x |

The treatment group details are provided in Table 2.

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

| Treatment name | Vaccine name | HBV Group |
|---|---|---|
| *Engerix-B Kinder* | HBV | • |

- Control: uncontrolled
- Vaccination schedule: A single dose of HBV vaccine will be administered to all subjects, who were previously primed and boosted with four doses of *Infanrix hexa* in the first two years of life.
- Treatment allocation: non-randomised

- Blinding: Refer to Table 3.

**Table 3 Blinding of study epochs**

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

- Sampling schedule: Blood samples will be taken from each subject at the following time-points:
  - Pre-vaccination: at Visit 1, before the administration of the single challenge dose of HBV vaccine.
  - Post-vaccination: at Visit 2, approximately one month after the single challenge dose of HBV vaccine.
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF).

# 3. OBJECTIVES

## 3.1. Primary objective

- To assess the immunological response to hepatitis B antigen, in terms of antibody concentrations ≥100 mIU/ml, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.

## 3.2. Secondary objectives

- To assess the persistence of anti-HBs antibodies, in terms of seroprotection status and antibody concentrations, in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.
- To assess the immunological response to hepatitis B antigen, in terms of anamnestic response, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.
- To assess the immunological response to the hepatitis B antigen, in terms of seroprotection status and antibody concentrations, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.
- To evaluate the safety and reactogenicity of a single challenge dose of HBV vaccine (Engerix-B Kinder) in terms of solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

# 4. ENDPOINTS

## 4.1. Primary endpoint

- Immunogenicity to components of the study vaccine.
  - Anti-HBs antibody concentrations ≥100 mIU/ml, one month after the single challenge dose of HBV vaccine.

## 4.2. Secondary endpoints

- Anti-HBs antibody persistence after previous vaccination with *Infanrix hexa.*
  - Anti-HBs antibody concentrations ≥ 10 mIU/ml, ≥ 100 mIU/ml and anti-HBs antibody concentrations before the single challenge dose of HBV vaccine.
- Immunogenicity to the components of the study vaccine.
  - Anti-HBs antibody concentrations ≥ 10 mIU/ml and anti-HBs antibody concentrations one month after the single challenge dose of HBV vaccine.
  - Anamnestic response to the single challenge dose of HBV vaccines.
- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom during the 4-day (Day 0–3) follow-up period after the single challenge dose of HBV vaccine.
- Unsolicited adverse event
  - Occurrence of unsolicited AEs during the 31-day (Day 0–30) follow-up period after the single challenge dose of HBV vaccine.
- Serious adverse event
  - Occurrence of serious adverse events after the single challenge dose of HBV vaccine up to study end.

# 5. ANALYSIS SETS

## 5.1. Definition

Three cohorts are defined for the purpose of analyses:

- Total vaccinated cohort (TVC)
- According To Protocol (ATP) cohort for analyses of Immunogenicity

### 5.1.1. Total vaccinated cohort

The TVC will include all subjects who received the single challenge dose of HBV vaccine.

- The TVC for the analyses of safety will include all subjects with study vaccine administration documented.
- The TVC for the analyses of immunogenicity will include all subjects who have received a single challenge dose of HBV vaccine and for whom data concerning immunogenicity endpoint measures are available.

### 5.1.2. According-to-protocol cohort for analyses of immunogenicity

The ATP cohort for analysis of immunogenicity will include all subjects who satisfy the below criteria:

- who meet all eligibility criteria
- who comply with the procedures and intervals defined in the protocol.
- who do not meet any of the elimination criteria during the study
- for whom post-vaccination immunogenicity (Visit 2) results are available.

The interval between vaccination at Visit 1 and blood sampling at Visit 2, considered for inclusion of a subject in the ATP cohort for analyses of immunogenicity will be 21-48 days.

## 5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each set below.

### 5.2.1. Elimination from Total Vaccinated Cohort

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from TVC.

### 5.2.2. Elimination from ATP cohort for analyses of Immunogenicity

#### 5.2.2.1. Excluded subjects

A subject will be excluded from the ATP analysis under the following conditions

| Code | Condition under which the code is used |
|---|---|
| 900 | Invalid informed consent or fraud data |
| 1030 | Study vaccine not administered at all |
| 1040 | Administration of concomitant vaccine(s) forbidden in the protocol |
| 1070 | Administration not according to protocol for reason specified by the investigator, other than side, site and route. |
| 1080 | Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by Status QA GMP NON Use. |
| 1090 | Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration. |
| 2010 | Protocol violation linked to the inclusion/exclusion criteria including age. |
| 2040 | Administration of any concomitant medication forbidden by the protocol. |
| 2050 | Underlying medical condition identified after dose 1 and forbidden by the protocol. |
| 2060 | Concomitant infection after dose 1 which is related to the vaccine which may influence immune response ie Subjects with evidence of hepatitis B infection or disease as identified by anti-HBc at visit 2 |
| 2070 | Concomitant infection after dose 1 which is not related to the vaccine which may influence immune response (e.g. Hepatitis infection in a lyme study) |
| 2090 | *Blood sample taken but*: non compliance with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS/vaccination dates) blood sample should be taken within 21-48 days post dose 1. |
| 2100 | Serological results not available for all antigens (ie anti-HBs and anti-HBc) POST vaccination (including lost samples, blood sample not done, unable to test, and absence of parallelism). |
| 2120 | Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results, wrong sample labelling) |

#### 5.2.2.2. Right censored Data

NA

#### 5.2.2.3. Visit-specific censored Data

NA

## 5.3. Important protocol deviation not leading to elimination from ATP cohort

The following important protocol deviations will be reported:

- In case of unexpected vaccinations at study start was granted due to regulatory recommendation, the subjects who had such vaccination could be mentioned.
- Subjects attending visit 2 alone without parents being present.
- Protocol deviations related to informed consent and not leading to eliminations.

# 6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in annex 1 and will not be repeated below. All Confidence Interval (CI) will be two-sided 95% CI.

## 6.1. Demography

### 6.1.1. Analysis of demographics/baseline characteristics planned in the protocol

The following calculations will be performed:

- The distribution of subjects enrolled among the study centres will be tabulated.
- The numbers of subjects who withdraw from the study will be tabulated according to the reason for drop-out.
- The deviations from specifications for age and intervals between study visits will be tabulated.
- The median, mean, range and standard deviation of age (in years) at the Visit 1. The median, mean and standard deviation of height (in centimeters), weight (in kilograms) and BMI (in kilograms per meter square) at Visit 1 will be computed. The racial and sex composition will be presented.
- Number and reason for elimination from ATP cohort will be tabulated.

### 6.1.2. Additional considerations

All demography summaries will be generated for the TVC. The summary of age, height, weight, BMI, race and sex composition will also be provided for the ATP cohort for Immunogenicity.

## 6.2. Exposure

### 6.2.1. Analysis of exposure planned in the protocol

NA

### 6.2.2. Additional considerations

The number of subjects who received the challenge dose will be tabulated.

## 6.3. Immunogenicity

### 6.3.1. Analyses for antibody persistence and response to challenge dose

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

- Prior to the single dose of HBV vaccine and one month after the single challenge dose of HBV vaccine:
  - Percentage of subjects with anti-HBs antibody concentrations ≥ 6.2 mIU/ml (seropositive), ≥ 10 mIU/ml and ≥ 100 mIU/ml, with exact 95% CI will be calculated [Clopper, 1934].
  - GMCs with 95% CI will be calculated for anti-HBs antibodies.
  - The distribution of anti-HBs antibody concentrations will be displayed using RCCs.
- The percentage of subjects with anti-HBs concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml, and ≥ 100 mIU/ml (with exact 95% CI [Clopper, 1934]) and GMCs at the post-HBV challenge dose time-point, in relation to their pre-challenge dose status (< 6.2 mIU/ml, ≥ 6.2 mIU/ml - < 10 mIU/ml, ≥ 10 mIU/ml) will be tabulated.
- Percentage of subjects (with 95% CI [Clopper, 1934]) who mount an anamnestic response to the single challenge dose of HBV vaccine will be calculated overall and in relation to their pre-vaccination status (< 6.2 mIU/ml, ≥ 6.2 mIU/ml - < 10 mIU/ml, ≥ 10 mIU/ml).
- Post-challenge anti-HBs antibody concentrations as a function of pre-challenge concentrations, with regression line will be computed using linear regression method for ATP cohort for immunogenicity. The model will include pre-challenge log transformed concentrations as regressor (independent or explanatory variable) and post-challenge log-transformed concentrations as an outcome (dependent or response) variable.antibody concentrations observed at the pre-challenge dose time point will be presented graphically.

### 6.3.2. Additional considerations

NA

## 6.4. Analysis of safety

### 6.4.1. Analysis of safety & reactogenicity planned in the protocol

The primary analyses of safety and reactogenicity will be based on the TVC.

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 4-day (Day 0 to Day 3) follow-up period after the vaccination will be tabulated with exact 95% CI [Clopper, 1934]. The same calculations will be performed for any Grade 3 (solicited or unsolicited) symptoms, relationship to the vaccination and any symptoms requiring medical attention.
- The percentage of subjects reporting each individual solicited symptom during the 4-day follow-up period with exact 95% CI [Clopper, 1934], by type of adverse event; by severity (any grade, Grade 3 only); by relationship to vaccination (any relationship, related only) and any symptoms requiring medical attention will be tabulated.
- The occurrence of fever will be tabulated per 0.5°C cumulative increments as well as the occurrence of Grade 3 fever (> 39.0 °C axillary temperature) with causal relationship to vaccination.
- The percentage of subjects with at least one report of unsolicited adverse event classified by the Medical Dictionary for Regulatory Activities and reported within the 31-day (Day 0 to Day 30) follow-up period after vaccination will be tabulated with exact 95% CI [Clopper, 1934]. The same tabulation will be performed for Grade 3 unsolicited adverse events, for unsolicited adverse events with a causal relationship to vaccination, and for unsolicited adverse events requiring medical attention.
- The percentage of subjects who started receiving at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day and 31-day follow-up period after vaccination will be tabulated (with exact 95% CI) [Clopper, 1934].
- SAEs and withdrawals due to AEs and SAEs reported during the study will be described in detail

### 6.4.2. Additional considerations

#### 6.4.2.1. Combined Solicited and Unsolicited Adverse Events

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA as per the following codes.

| Solicited symptom | Lower level term code | Corresponding Lower level term decode |
|---|---|---|
| PA | 10022086 | Injection site pain |
| RE | 10022098 | Redness at injection site |
| SW | 10053425 | Swelling at injection site |
| FA | 10016256 | Fatigue |
| TE | 10016558 | Fever |
| GI | 10017944 | Gastrointestinal disorder |
| HE | 10019211 | Headache |

# 7. ANALYSIS INTERPRETATION

All analyses are descriptive.

# 8. CONDUCT OF ANALYSES

## 8.1. Sequence of analyses

The analyses will be performed when all data up to one month after the vaccine dose will be available. All analyses and associated individual data will be presented in a Clinical Study Report, which will be shared with the investigator(s) involved in the conduct of this study.

| Description | Analysis ID | Disclosure Purpose (CTRS=public posting, SR=study report, internal, public posting) | Dry run review needed (Y/N) | Study Headline Summary (SHS)requiring expedited communication to upper management (Yes/No) | Reference for TFL |
|---|---|---|---|---|---|
| Analysis of epoch 1 | E1_01 | SR | Yes | Yes | TFL TOC Statistical peer review version - All TFLs |

## 8.2. Statistical considerations for interim analyses

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

# 9. CHANGES FROM PLANNED ANALYSES

The major changes from the protocol are,

- According-to-protocol cohort for analyses of antibody persistence defined in the protocol for the analysis of antibody persistence was removed from the SAP to reduce the number of cohorts used in the analysis. The analysis of persistence and response to challenge dose will be performed on the According-to-protocol cohort for analyses of immunogenicity. This change will not have significant impact on the analysis of persistence as no major difference in number of subjects expected between the ATP cohort for analysis of Immunogenicity and ATP cohort for analyses of antibody persistence.

Other changes include,

- The analysis for persistence and response to challenge dose is harmonized with respect to the cut-offs to consider.
    - The analysis to summarize the number and percentage of subjects between >10 mIU/mL and < 100 mIU/mL planned in the protocol was removed to be consistent with the endpoints of the study.
    - The analysis to summarize the post challenge dose response and anamnestic response stratified by the pre-challenge dose concentrations will be performed by considering the categories < 6.2 mIU/ml, ≥ 6.2 mIU/ml - < 10 mIU/ml, and ≥ 10 mIU/ml at pre-challenge dose time point.
- All the analysis of solicited and/or unsolicited adverse events will be performed for any, grade 3, by relationship to vaccination, and requiring medical attention to be consistent with the presentation of the adverse events summary.

# 10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The following group name will be used in the TFLs, to be in line with the treatment dataset:

| Group order in tables | Group label in tables | Group definition for footnote | Pooled Groups label in tables | Pooled definition for footnote |
|---|---|---|---|---|
| 1 | HBV Group | Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study | HBV Group | HBV Group |

# 11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

## 11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934;26:404-413].

## 11.2. Standard data derivation

### 11.2.1. Date derivation

- SAS date derived from a character date: in case day is missing, 15 is used. In case day & month are missing, 30June is used.
- Onset day for an event (AE, medication, vaccination...): the onset day is the number of days between the last study vaccination & the onset/start date of the event. This is 0 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.

### 11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. Specifically in this study, dose 1 refers to all vaccines administered at the first vaccination visit.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose.

### 11.2.3. Demography

- Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity.

### 11.2.4. Immunogenicity

- A seronegative subject is a subject with anti-HBs antibody concentration below the assay cut-off (< 6.2 mIU/ml).
- A seropositive subject is a subject with anti-HBs antibody concentrations above the assay cut-off (≥ 6.2 mIU/ml).

- A seroprotected subject is a subject with anti-HBs antibody concentrations above the protection level (≥ 10 mIU/ml).
- Anamnestic response to the single challenge dose is defined as:
  - At least (i.e. greater than or equal to) 4-fold rise in post-vaccination anti-HBs antibody concentrations in subjects seropositive at the pre-vaccination time point.
  - Post-vaccination, anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects seronegative at the pre-vaccination time point.
- The Geometric mean antibody concentrations (GMCs) calculations will be performed by taking the anti-log of the mean of the $\log_{10}$ concentration transformations. All subjects will be considered. Subjects whose antibody concentrations are below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation. Note that as per assay specification, results between the assay cut-off of 6.2 mIU/ml and 7.65 mIU/ml (= Lower limit of Quantification) will be quantified as 6.2 mIU/ml.
- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- All CI computed will be two-sided 95% CI.

### 11.2.5. Safety/Reactogenicity

- For the analyses of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analyses of the solicited symptoms based on the TVC will include only subjects with documented safety data (i.e. symptom screen completed).
- For the analyses of unsolicited adverse events/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.
- The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

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

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

| Axillary | | |
|---|---|---|
| 0 | : | < 37.5°C |
| 1 | : | ≥37.5°C and ≤ 38.0°C |
| 2 | : | > 38.0°C and ≤ 39.0°C |
| 3 | : | > 39.0°C |

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value may differ from one table to another.

| Event | N used for deriving % per subject for Vaccination phase |
|---|---|
| Solicited general symptom | All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed) |
| Solicited local symptom | All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed) |
| Unsolicited symptom | All subjects with study vaccine administered |
| Concomitant medication | All subjects with study vaccine administered |

### 11.2.6. Management of missing data

**Demography:**

- For a given subject and a given demographic variable, missing measurements will not be replaced.

**Immunogenicity:**

- For a given subject and a given immunogenicity measurement time point, missing or non-evaluable measurements will not be replaced.

**Reactogenicity and safety:**

- Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

### 11.2.7. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

| Display Table | Parameters | Number of decimal digits |
|---|---|---|
| Demographic characteristics | Mean, median age | 1 |
| Demographic characteristics | SD (age) | 1 |
| Immunogenicity | Anti-HBs GMC, including LL & UL of CI | 1 |
| All summaries | % of count, including LL & UL of CI | 1 |

## 12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to Section 5.2.

# 13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used.

The data display, title and footnote are for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC.

These templates were copied from DTPa-HBV-IPV-114 (106793) and additional tables required for public disclosure were added. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs. These editorial/minor changes will not lead to a SAP amendment.

### Template 1 Minimum and maximum activity dates (Total vaccinated cohort)

| Activity number | Activity Description | Minimum date | Maximum date |
|---|---|---|---|
| 10 | VISIT 1 | | |
| 20 | VISIT 2 | | |

### Template 2 Number of subjects by center (Total vaccinated cohort)

| | HBV Group | |
|---|---|---|
| **Center** | **n** | **%** |
| PPD | | |
| | | |
| | | |
| | | |
| ... | | |
| ... | | |
| All | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals' assigned center number

## Template 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

| | HBV Group |
|---|---|
| **Number of subjects vaccinated** | |
| **Number of subjects completed** | |
| **Number of subjects withdrawn** | |
| Reasons for withdrawal : | |
| Serious Adverse Event | |
| Non-Serious Adverse Event | |
| Protocol violation | |
| Consent withdrawal (not due to an adverse event) | |
| Migrated/moved from study area | |
| Lost to follow-up (subjects with incomplete vaccination course) | |
| Lost to follow-up (subjects with complete vaccination course) | |
| Sponsor study termination | |
| Other | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit

## Template 4 Number of subjects at each visit and list of withdrawn subjects (Total vaccinated cohort)

| Group | VISIT | N | Withdrawn Subject numbers | Reason for withdrawal |
|---|---|---|---|---|
| HBV Group | VISIT 1 | | | |
| | | | | |
| | | | | |
| | VISIT 2 | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = Number of subjects who are still in the study up to the visit
Withdrawn = Subject who did not return after the visit

## Template 5 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

| Title | HBV Group | | |
|---|---|---|---|
| | n | s | % |
| **Total cohort** | | | |
| Invalid informed consent or fraud data (code 900) | | | |
| Study vaccine dose not administered AT ALL but subject number allocated (code 1030 ) | | | |
| **Total vaccinated cohort** | | | |
| Administration of vaccine(s) forbidden in the protocol (code 1040 ) | | | |
| Study vaccine dose not administered according to protocol (code 1070 ) | | | |
| Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090 ) | | | |
| Essential serological data missing (code 2100 ) | | | |
| Obvious incoherence or abnormality or error in data (code 2120 ) | | | |
| **ATP cohort for analysis of immunogenicity** | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided where:
n= number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s= number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Codes are listed based on a ranking order

## Template 6 Deviations from specifications for age and intervals between study visits (Total vaccinated cohort)

| | | Age | VAC:1-SER:2 |
|---|---|---|---|
| **Group** | | **Protocol** | **Protocol** |
| | | from 14-15 Years | from 21 to 48 days |
| HBV Group | N | | |
| | n | | |
| | % | | |
| | range | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for intervals
Age = Age computed at challenge dose
VAC: 1= Vaccination at visit 1
SER: 2= Blood sampling at visit 2

## Template 7 Summary of demographic characteristics (Total vaccinated cohort)

| | | HBV Group N = XXX | |
|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** |
| Age (Years) at challenge dose | Mean | | |
| | SD | | |
| | Median | | |
| | Minimum | | |
| | Maximum | | |
| Gender | Female | | |
| | Male | | |
| Geographic Ancestry | African Heritage / African American | | |
| | American Indian or Alaskan Native | | |
| | Asian - Central / South Asian Heritage | | |
| | Asian - East Asian Heritage | | |
| | Asian - Japanese Heritage | | |
| | Asian - South East Asian Heritage | | |
| | Native Hawaiian or Other Pacific Islander | | |
| | White - Arabic / North African Heritage | | |
| | White - Caucasian / European Heritage | | |
| | Other | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

## Template 8 Summary of vital signs characteristics (Total vaccinated cohort)

| | | HBV Group (N = xxx) |
|---|---|---|
| **Characteristics** | **Parameters** | **Value** |
| Height (cm) | Mean | |
| | SD | |
| | Median | |
| | Minimum | |
| | Maximum | |
| | Unknown | |
| Weight (kg) | Mean | |
| | SD | |
| | Median | |
| | Minimum | |
| | Maximum | |
| | Unknown | |
| BMI (kg/m²) | Mean | |
| | SD | |
| | Median | |
| | Minimum | |
| | Maximum | |
| | Unknown | |

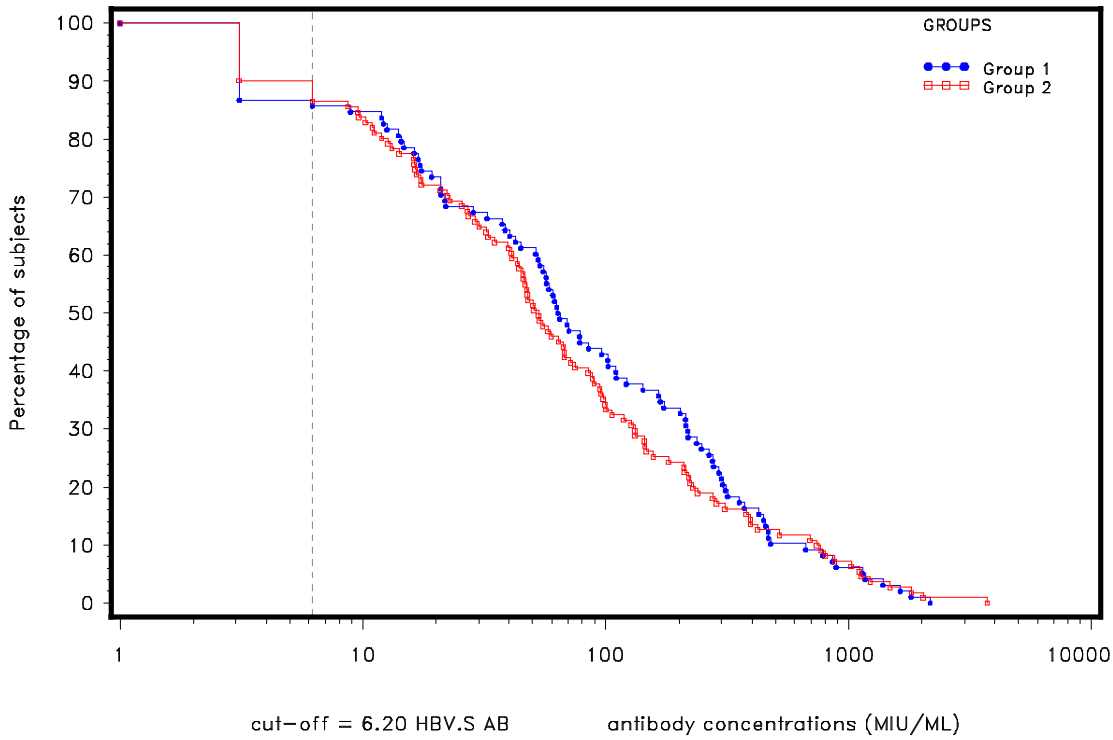
HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Height (cm) =Height expressed in centimetres
Weight (kg) =Weight expressed in kilograms
BMI (kg/m²) = Body Mass Index in kilograms per meter square

## Template 9 Percentage of subjects with antibody concentrations ≥ 6.2 mIU/mL, ≥ 10 mIU/mL, ≥ 100 mIU/mL and GMCs for anti-HBs antibody concentrations with 95% CI at pre-challenge dose and one month after the challenge dose (ATP cohort for analysis of immunogenicity)

| Group | Timing | N | ≥ 6.2 mIU/mL | | | | ≥ 10 mIU/mL | | | | ≥ 100 mIU/mL | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | 95% CI | | n | % | 95% CI | | | | 95% CI | | Value | 95% CI | |
| | | | | | LL | UL | | | LL | UL | n | % | LL | UL | | LL | UL |
| HBV Group | Pre | | | | | | | | | | | | | | | | |
| | P1(D30) | | | | | | | | | | | | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre: Blood sampling at pre-challenge dose time point
P1(D30): Blood sampling one month after the challenge dose

## Template 10 Reverse cumulative distribution curve of anti-HBs antibody concentrations at <pre-challenge dose/one month after the challenge dose> (ATP cohort for analysis of immunogenicity)




HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
Note: The groups shown in figure are indicative only. Actual groups may differ.

## Template 11 Percentage of subjects with antibody concentrations ≥ 6.2 mIU/mL, ≥ 10 mIU/mL, ≥ 100mIU/mL and GMCs for anti-HBs antibody concentrations stratified based on the pre-challenge dose status (ATP cohort for analysis of immunogenicity)

| | | | | ≥ 6.2 mIU/mL | | | | ≥ 10 mIU/mL | | | | ≥ 100 mIU/mL | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | 95% CI | | | | 95% CI | | | | 95% CI | |
| Group | Pre-vaccination status | Timing | N | n | % | LL | UL | n | % | LL | UL | n | % | LL | UL | value | LL | UL |
| HBV Group | < 6.2 mIU/mL | Pre | | | | | | | | | | | | | | | | |
| | | P1(D30) | | | | | | | | | | | | | | | | |
| | ≥ 6.2 mIU/mL - <10 mIU/mL | Pre | | | | | | | | | | | | | | | | |
| | | P1(D30) | | | | | | | | | | | | | | | | |
| | ≥ 10mIU/mL | Pre | | | | | | | | | | | | | | | | |
| | | P1(D30) | | | | | | | | | | | | | | | | |
| | Overall | Pre | | | | | | | | | | | | | | | | |
| | | P1(D30) | | | | | | | | | | | | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre: Blood sampling at pre-challenge dose time point
P1(D30): Blood sampling one month after the challenge dose

## Template 12 Anamnestic response for anti-HBs antibodies at one month after the challenge dose (ATP cohort for analysis of immunogenicity)

| | | | Anamnestic response to the challenge dose | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| **Group** | **Pre-vaccination status** | **N** | **n** | **%** | **LL** | **UL** |
| HBV Group | S- | | | | | |
| | S+ | | | | | |
| | Total | | | | | |

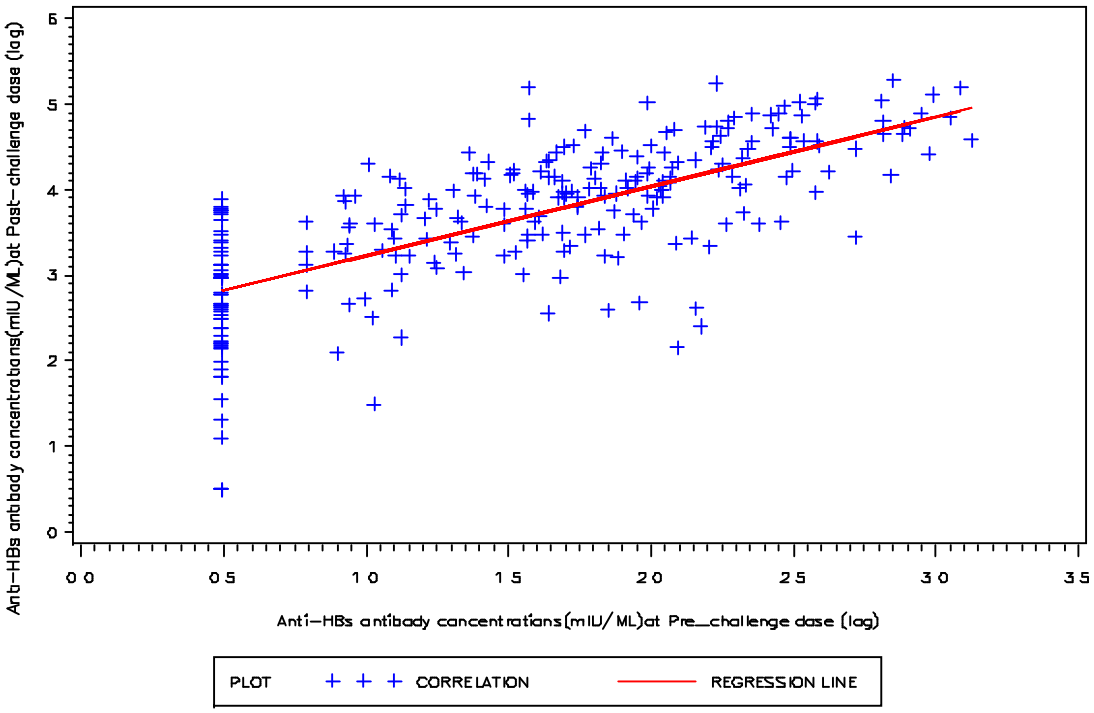
HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
S- = seronegative subjects (antibody concentration < 6.2mIU/mL for anti-HBs) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 6.2mIU/mL for anti-HBs) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination Challenge Dose response is defined as:
For initially seronegative subjects, antibody concentration greater than or equal to 10mIU/mL (≥10mIU/mL )
For initially seropositive subjects: antibody concentration at least four times the pre-challenge antibody concentration
N = number of subjects with both pre- and post-vaccination results available
n(%) = number(percentage) of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

## Template 13 Anamnestic response for anti-HBs antibodies at one month after the challenge dose stratified based on the pre-challenge dose status (ATP cohort for analysis of immunogenicity)

| | | | Anamnestic response to the challenge dose | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| **Group** | **Pre-vaccination status** | **N** | **n** | **%** | **LL** | **UL** |
| HBV Group | < 6.2 mIU/mL | | | | | |
| | ≥ 6.2 mIU/mL - <10 mIU/mL | | | | | |
| | ≥ 10mIU/mL | | | | | |
| | Total | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
S- = seronegative subjects (antibody concentration < 6.2mIU/mL for anti-HBs) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 6.2mIU/mL for anti-HBs) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination Challenge Dose response defined as:
For initially seronegative subjects, antibody concentration greater than or equal 10mIU/mL (≥10mIU/mL )
For initially seropositive: antibody concentration at least four times the pre-vaccination antibody concentration
N = number of subjects with both pre- and post-vaccination results available
n(%) = number(percentage) of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

## Template 14 Anti-HBs antibody concentrations post challenge as a function of pre-challenge concentrations, with regression line (ATP cohort for analysis of immunogenicity)




Regression equation and $R^2$ is given by
y= (a)+(b)x
$R^2$ =(c)
Where,
y= post challenge dose (log)
x= pre challenge dose (log)
R2 = proportion of variation in post challenge dose (log) that is predictable from pre challenge dose (log)
$R^2$=(c) may be interpreted as follows: "(c) % of the variation in response variable is explained by regressors or regressors predict response variable by (c) %"

## Template 15 Number and percentage of subjects who received study vaccine dose (Total vaccinated cohort)

| | HBV Group N = XXX | |
|---|---|---|
| **Total number of doses received** | **n** | **%** |
| 1 | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = number of subjects in group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses

## Template 16 Compliance in returning symptom information (Total vaccinated cohort)

| Group | Number of doses | Doses NOT according to protocol | Number of general SS | Compliance % general SS | Number of local SS | Compliance % local SS |
|---|---|---|---|---|---|---|
| HBV Group | | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

## Template 17 Percentage of subjects reporting either solicited symptoms or unsolicited adverse events during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

| | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| Group | N | N | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| HBV Group | | | | | | | | | | | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = number of subjects with administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

## Template 18 Percentage of subjects reporting solicited local symptoms during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

| | | HBV Group | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL |
| Pain | All | | | | | |
| | Grade 3 | | | | | |
| | Medical advice | | | | | |
| Redness | All | | | | | |
| | > 50 mm | | | | | |
| | Medical advice | | | | | |
| Swelling | All | | | | | |
| | > 50 mm | | | | | |
| | Medical advice | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = number of subjects with documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Grade 3 For Pain: severe: Significant pain at rest. Prevented normal everyday activities
For Redness/Swelling: > 50mm

## Template 19 Percentage of subjects reporting solicited general symptoms during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

| | | HBV Group | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95 % CI | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** |
| Fatigue | All | | | | | |
| | Grade 3 | | | | | |
| | Related | | | | | |
| | Medical advice | | | | | |
| Gastrointestinal symptoms | All | | | | | |
| | Grade 3 | | | | | |
| | Related | | | | | |
| | Medical advice | | | | | |
| Headache | All | | | | | |
| | Grade 3 | | | | | |
| | Related | | | | | |
| | Medical advice | | | | | |
| Temperature/(Oral) (°C) | All | | | | | |
| | ≥37.5 | | | | | |
| | >38.0 | | | | | |
| | >38.5 | | | | | |
| | >39.0 | | | | | |
| | Related | | | | | |
| | >39.0 Related | | | | | |
| | Medical advice | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = number of subjects with documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Grade 3 For Headache: Headache that prevented normal activity
For Temperature: > 39.0°C
For Fatigue: Fatigue that prevented normal activity
For Gastrointestinal symptoms: Gastrointestinal symptoms that prevented normal activity

## Template 20 Percentage of subjects reporting the occurrence of unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HBV Group N = XXX | | | |
|---|---|---|---|---|---|
| | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | | | | |
| Blood and lymphatic system disorders (10005329) | Leukocytosis (10024378) | | | | |
| Cardiac disorders (10007541) | Angina unstable (10002388) | | | | |
| | Mitral valve disease (10061532) | | | | |
| | Myocardial infarction (10028596) | | | | |
| Respiratory, thoracic and mediastinal disorders (10038738) | Pleural effusion (10035598) | | | | |
| | Pneumothorax (10035759) | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

## Template 21 Number (%) of subjects reporting serious adverse events during the whole study period including number of events reported (Total vaccinated cohort)

| | | | Gr 1 N = | | | Gr2 N = | | |
|---|---|---|---|---|---|---|---|---|
| **Type of Event** | **Primary System Organ Class** | **Preferred Term (CODE)** | **n*** | **n** | **%** | **n*** | **n** | **%** |
| SAE | At least one symptom | | | | | | | |
| | <each SOC> | <each PT term> | | | | | | |
| Related SAE | At least one symptom | | | | | | | |
| | <each SOC> | <each PT term> | | | | | | |
| Fatal SAE | At least one symptom | | | | | | | |
| | <each SOC> | <each PT term> | | | | | | |
| Related fatal SAE | At least one symptom | | | | | | | |
| | <each SOC> | <each PT term> | | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

## Template 22 Number and percentage of subjects starting a concomitant medication during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

| | HBV Group | | | | |
|---|---|---|---|---|---|
| | | | | 95% CI | |
| | N | n | % | LL | UL |
| Any | | | | | |
| Any antipyretic | | | | | |
| Prophylactic antipyretic | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = number of subjects with administered dose
n/% = number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period

## Template 23 Listing of SAEs (Total vaccinated cohort)

| Group | Sub. No. | Age at onset (Year) | Sex | Verbatim | Preferred term | System Organ Class | MED type | Dose | Day of onset | Duration | Intensity | Causality | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HBV Group | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study

## Template 24 Listing of dropouts from the study due to AEs, SAEs and solicited symptoms (Total vaccinated cohort)

| Group | Study-Subject No. | Country | Gender | AE Description | SAE | Causality | Outcome | Type of discontinuation |
|---|---|---|---|---|---|---|---|---|
| HBV Group | | | | | | | | |
| | | | | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study

## Template 25 Study population (Total vaccinated cohort)

| Number of subjects | HBV Group |
|---|---|
| Planned, N | |
| Randomised, N (Total vaccinated cohort) | |
| Completed n (%) | |
| **Demographics** | **HBV Group** |
| N (Total vaccinated cohort) | |
| Females: Males | |
| Mean Age(At challenge dose), years (SD) | |
| Median Age, years (minimum, maximum) | |
| White - Caucasian / European Heritage, n (%) | |
| White - Arabic / North African Heritage, n (%) | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
SD - Standard Deviation
N - Total number of subjects enrolled in the study
n (%) - Number (percentage) of subjects in a given category

## Template 26 Solicited and Unsolicited symptoms experienced by at least 5 % of subjects classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination - SAE excluded (Total Vaccinated cohort)

| | | HBV Group N = XXX | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n*** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | | | | | |
| Blood and lymphatic system disorders (10005329) | Leukocytosis (10024378) | | | | | |
| Cardiac disorders (10007541) | Angina unstable (10002388) | | | | | |
| | Mitral valve disease (10061532) | | | | | |
| | Myocardial infarction (10028596) | | | | | |
| Respiratory, thoracic and mediastinal disorders (10038738) | Pleural effusion (10035598) | | | | | |
| | Pneumothorax (10035759) | | | | | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/%,= number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

## Template 27 Number of subjects by country

| | HBV Group N = xxx |
|---|---|
| **Country** | **N** |
| Xxxxx | |
| Xxxxx | |
| Xxx | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = number of subjects
n= number of enrolled subjects included in each group

## Template 28 Number of enrolled subjects by age category

| | | HBV Group N = |
|---|---|---|
| **Characteristics** | **Categories** | **n** |
| Age category | In utero | |
| | Preterm newborn infants (gestational age < 37 wks) | |
| | Newborns (0-27 days) | |
| | Infants and toddlers (28 days-23 months) | |
| | Children (2-11 years) | |
| | Adolescents (12-17 years) | |
| | Adults (18-64 years) | |
| | From 65-84 years | |
| | 85 years and over | |
| | Missing | |

HBV Group= Subjects who previously received 4 doses of Infanrix hexa in first two years of life and received a challenge dose of HBV vaccine in this study
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories
Missing = <describe missing>