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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase 1, multicentre, long term follow-up study up to 4 years after study vaccination to assess immunogenicity and safety of the investigational GSK Biologicals' GSK3277511A vaccine in adults.
eTrack study number and Abbreviated Title	204913 (NTHI-MCAT-006 EXT:001)
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 24-OCT-2017
Co-ordinating author:	PPD (Statistician), PPD (Statistician)
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14April 2017)

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LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AS	Adjuvant System
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EU/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
GMC	Geometric mean antibody concentration
GMR	Geometric mean ratio
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IU/ml	International units per milliliter
LAR	Legally acceptable representative
LL	Lower Limit of the confidence interval
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PD	Protein D
PE	Protein E
PilA	Type IV pili subunit
pIMD	Potential immune-mediated disease
PPS	Per Protocol Set
SAE	Serious adverse event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SHS	Study Headline Summary

SPM	Study Procedures Manual
SR	Study Report
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
UspA2	Ubiquitous surface protein A2 of Moraxella catarrhalis
µg	Microgram

1. DOCUMENT HISTORY

Date	Description	Protocol Version
04-JUL-2017	*first version*	Protocol 10-February-2017
24-OCT-2017	*Amendment 1*	

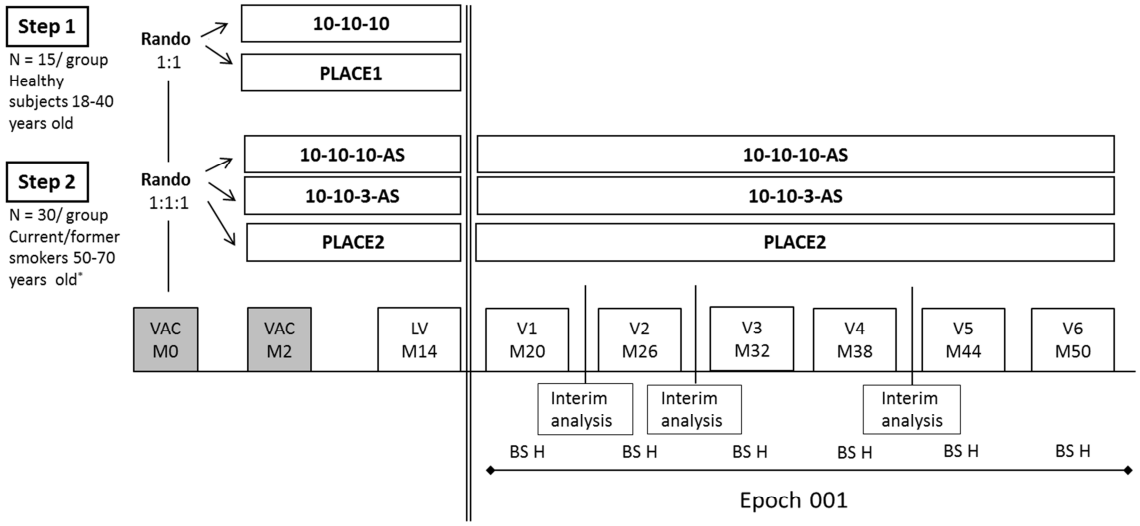
2. STUDY DESIGN

This is a phase 1, controlled, multi-centric, single-country, long term follow-up study with three parallel groups from NTHi-Mcat-001 study.

Only the subjects included in STEP 2 of the primary vaccination study (NTHi-Mcat-001/ 201281) will be enrolled in this follow-up study.

STEP 2 of the NTHi-Mcat-001 study included 90 healthy adults, 50–71 years old at the time of enrolment, with a smoking history of at least 10 pack-years, either receiving placebo as control, or one of two AS01E adjuvanted formulations, i.e. 10 µg of PD, 10 µg of PE-PilA and 10 µg of UspA2 (Group 10-10-10-AS) or 10 µg of PD, 10 µg of PE-PilA and 3.3 µg of UspA2 (Group 10-10-3-AS).

Figure 1 Study Design Overview



BS H = blood sample for humoral immune responses;
Rando = randomisation; **LV**= Last Visit of NTHi-Mcat-001 study; **V** = Visit of NTHi-Mcat-006 study ; **M** = Month; **VAC** = vaccination (indicated in grey);
* With a cigarette smoking history ≥10 pack-years (calculation pack-years = average number of cigarettes smoked per day x number of years smoked)/20

- Study groups of NTHi-Mcat-001 study:
  - **10-10-10-AS**: Up to 30 subjects who have received two doses of the AS01E-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine during STEP 2 of NTHi-Mcat-001 study containing 10µg of PD, PE-PilA and UspA2.
  - **10-10-3-AS**: Up to 30 subjects who have received two doses of the AS01E-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine during STEP 2 of NTHi-Mcat-001 study containing 10µg of PD, 10µg of PE-PilA, and 3.3µg of UspA2.
  - **PLACE2**: Up to 30 subjects who have received two doses of placebo (saline solution) during STEP 2 of the NTHi-Mcat-001 study.

Since NTHI-MCAT-006 is a follow up study, group names and characteristics will be identical to parent study NTHi-Mcat-001. No vaccine will be administered in this trial.

3. OBJECTIVES

3.1. Primary objective

- To assess the persistence of humoral antibodies up to 3 years after the last planned visit (Month 14) in the NTHi-Mcat-001 study.

3.2. Secondary objective

- To assess the safety of the investigational NTHi-Mcat vaccine in terms of serious adverse events (SAE) and potential immune-mediated diseases (pIMD) up to 3 years after the last planned visit (Month 14) in the NTHi-Mcat-001 study.

4. ENDPOINTS

4.1. Primary endpoint

- Humoral immune response to the components of the NTHi Mcat investigational vaccine formulations at Month 20, Month 26, Month 32, Month 38, Month 44 and Month 50 in all subjects:
  - Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations.

4.2. Secondary endpoints

- Occurrence of any SAE, during the entire study period in all subjects.
- Occurrence of any pIMD during the entire study period in all subjects.

5. ANALYSIS SETS

5.1. Definition

Note that in order to align to ICH and CDISC terminology the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively.

5.1.1. Exposed Set

The ES for safety analysis will include all subjects from STEP 2 of NTHi-Mcat-001 (201281) enrolled in this follow-up study.

The ES for immunogenicity analysis will include all subjects from STEP 2 of NTHi-Mcat-001 (201281) enrolled in this follow-up study and for whom immunogenicity data are available.

5.1.2. Per-protocol Set

The PPS will consist of all subjects from the ES who will comply with eligibility criteria, study procedures up to the last subject last visit and had immunogenicity results in the epoch.

More specifically, the PPS will include all eligible subjects:

- Who met all eligibility criteria.
- Who did not receive a concomitant medication/ product/vaccine leading to the elimination from the Per Protocol analysis.
- Who did not present with an intercurrent medical condition leading to elimination from the Per Protocol analysis.
- Who complied with at least one of the immunogenicity blood sample timings.
- For whom immunogenicity results are available for at least one assay in at least one of the follow-up time points.

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.

5.2.1. Elimination from Exposed Set

Code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Per-protocol analysis Set

5.2.2.1. Excluded subjects

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

Table 1 Elimination Codes[1]

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1040	Administration of concomitant vaccine forbidden in the protocol: any investigational or non-registered vaccine used during the study period.
2010	Protocol violation (inclusion/exclusion criteria) Inclusion: • Subjects who previously participated in STEP 2 of study NTHi-Mcat-001 (201281), and performed the last study visit (Month 14) and received the 2 study vaccinations. • Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. return for follow-up visits). And subjects' Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol. • Written informed consent obtained from the subject/ LAR(s) of the subject prior to performance of any study specific procedure. Exclusion: • Use of any investigational or non-registered product (drug or vaccine) during the period starting 30 days before the first follow-up study visit (Month 19 to Month 20), or planned use during the study period. • Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since the end of the NTHi-Mcat-001 study. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed. • Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab). • Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device). • Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first follow-up visit or planned administration during the study period. • Current alcoholism and/or drug abuse. • Has significant disease (including significant neurological or psychological disorders), in the opinion of the investigator, likely to interfere with the study and/or likely to cause death within the study duration.

[1] These will be identified during review of individual data listings

Code	Condition under which the code is used
	• Any other condition that the investigator judges may interfere with study findings.
2040	Administration of any medication forbidden by the protocol: • Any investigational or non-registered drug used during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day (for adult subjects), or equivalent. Inhaled and topical steroids are allowed. • Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab). • Immunoglobulins and/or any blood products administered during the study period.
2050	Underlying medical condition forbidden by the protocol: if, during the study, subjects incur a condition that has the capability of altering their immune response (i.e. confirmed immunosuppressive or immunodeficient condition, including HIV).
2060	Concomitant infection related to the vaccine which may influence immune response: infection related to any of the vaccine component.
2070	Concomitant infection not related to the vaccine which may influence immune response.
2090	Blood Sample taken but: non compliance with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS dates: -20/+20 days).
2100	Serological results not available for antigens POST vaccination (including lost samples, blood sample not done, unable to test, absence of parallelism). If results for **all** antigens are missing or unknown.
2110	Essential serological results temporarily missing because not tested yet (For interim analysis).
2120	Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results, wrong sample labelling).
2130	Subject not planned to be bled for their all blood sampling visits
2140	Temperature deviation from range defined in protocol and/or SPM and/or Lab Manual.

5.3. Important protocol deviation not leading to elimination from per-protocol cohort

The following important protocol deviations will be reported by groups:

- Short follow-up: subjects who completed the last study contact before the minimum length of follow-up requirement.
- In case of immunogenicity sub-set for different blood samples schedules, the subjects who follow an erroneous bleeding schedule could be mentioned.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and statistical methods are described in annex 1 and will not be repeated below.

6.1. Demography

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

Demographic characteristics (retrieved from parent study Nthi-Mcat-001) age at the first dose in years, gender, ethnicity, race, smoking/exposure history status, pulmonary function test baseline results, height, weight and a cohort description will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as race;
- Mean, median and standard deviation will be provided for continuous data such as age.

- The distribution of subjects enrolled among the study sites will be tabulated as a whole and per group.
- Withdrawal status will be summarised by group using descriptive statistics:
  - The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal.
- The number of subjects enrolled into the study as well as the number of subjects excluded from different population of analysis will be tabulated.

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the Per Protocol Set. If, in any study group, the percentage of enrolled subjects with serological results excluded from the Per Protocol Set for analysis of immunogenicity is 10% or more, a second analysis based on the Exposed Set for immunogenicity will be performed to complement the Per Protocol Analysis.

Within group assessment

For each group, at Visit 1 (Month 20), Visit 2 (Month 26), Visit 3 (Month 32), Visit 4 (Month 38), Visit 5 (Month 44) and Visit 6 (Month 50), when blood samples are available for humoral immune response and for each assay:

- Seropositivity rate and their exact 95% CI will be tabulated.
- Adjusted geometric mean concentrations (GMCs) and associated two-sided 95% confidence intervals (CIs) will be computed. These will be obtained from one-way ANCOVA with group as fixed effect and Visit 1 (Day 0) concentration in NTHi-Mcat-001 as regressor.
- Geometric Mean Ratios (GMRs) with respect to Visit 1 (Day 0) in NTHi-Mcat-001 will be calculated for Visit 1 (Month 20), Visit 2 (Month 26), Visit 3 (Month 32), Visit 4 (Month 38), Visit 5 (Month 44) and Visit 6 (Month 50), for each group.
- A graph of the GMCs across the time (Visit 1 (Month 20) to Visit 6 (Month 50)) will be considered. Measures such as the maximum concentration, the time of the peak of concentration will be computed. One graph per strain will be created. Each graph will show the 3 groups.
- For each strain, antibody concentrations distribution will be investigated using Reverse Cumulative Curves.
- Subject graphs of immunogenicity results over time will be provided.

These analyses will also be performed for each level of the following minimisation factor: age (50-59 years vs. 60-71years).

Between group assessment

Comparative analyses will be exploratory with the aim to characterise the difference between the 10-10-10-AS and 10-10-3-AS groups in humoral immune response.

At each visit, differences in percentages and two-sided 95% CIs between the groups 10-10-10-AS versus 10-10-3-AS, will be calculated and the associated confidence interval for the difference will be constructed using the standardised asymptotic method.

At each visit, the difference in terms of GMCs will be evaluated, by computing the 95% CIs of the GMC ratios between 10-10-AS and 10-10-3-AS groups, using a one-way ANCOVA model on the logarithm10 transformation of the concentrations. The ANCOVA model will include the group category as fixed effects and the Visit 1 (Day 0) concentration in NTHi-Mcat-001 study as regressor.

These differences should be interpreted with caution, considering that there will be no adjustment for multiplicity of endpoints.

Comparison with placebo

Placebo comparative analyses are planned to evaluate the prematurely stopping of the trial.

GMCs and GMC ratios, together with 95% CIs will be computed, at each visit, using a one-way ANCOVA model on the logarithm 10 transformation of the concentrations. The ANCOVA model will include the group category as fixed effects and the Visit 1 (at Day 0) concentration in NTHi-Mcat-001 study as regressor. The GMC ratios (vaccinated

versus placebo) point estimates obtained from ANCOVA model will be considered for the evaluation of stopping the trail.

6.3. Analysis of safety

6.3.1. Analysis of safety planned in the protocol

The safety analysis will be performed on the ES for safety and will include the analysis of the following categories of events:

- Serious Adverse Events (SAEs)
- pIMDs

All SAEs and pIMDs occurring at any time during the study will be recorded according to the protocol-specified reporting rules.

The verbatim reports of the symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate preferred term (PT). The number and the percentage of subjects who experienced at least one SAE with its exact 95% CI will be tabulated by group and by MedDRA PT. Same tabulation will be performed for subjects who experienced any pIMDs.

For the corresponding percentages, the denominator will be the respective numbers of exposed subjects.

SAEs or pIMDs related to the investigational vaccine administered in NTHi-Mcat-001 study, which were reported after last subject last visit of study NTHi-Mcat-001 and AFTER the subject signed the Informed Consent Form of NTHI-MCAT-006, have to be reported and included in the analyses of NTHI-MCAT-006 study.

The number of subjects who experienced any **SAE related to study participation or concurrent GSK medication/ vaccination,** from first visit up to study conclusion will be reported.

Deaths, and withdrawal due to SAE(s) reported during the entire study will be tabulated.

6.3.1.1. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects starting/reporting concomitant medications within the entire study period will be tabulated by group. A concomitant medications categorization will result from listings review meetings and will be considered in the summaries.

7. ANALYSIS INTERPRETATION

All analyses are descriptive. The use of these descriptive analyses should be limited to supportive analysis of confirmatory analyses or hypothesis generation.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Table 2 Sequence of Analysis

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)
Interim 1	E1_02	Internal	No
Interim 2	E1_03	Internal	No
Interim 3	E1_04	Internal	No
Final Analysis	E1_01	CTRS & Study report	Yes

8.2. Statistical considerations for interim analyses

Three interim analyses will be performed on all data obtained up to Month 20, Month 26 and Month 38, respectively. The study may be stopped if the GMC ratio (point estimate; Active [10-10-10-AS and 10-10-3-AS groups] versus PLACE2) for at least 2 out of 4 antigens is ≤ 2, conclusion of further blood draws and early stop of the trial may be considered. Therefore, 2 GMC ratios per antigen will be calculated: 10-10-10-AS versus PLACE2, and 10-10-3-AS versus PLACE2.

- The analysis of data up to Visit 1 (Month 20) will be performed in a first step for Interim 1. This analysis will include:
  - The analysis of primary objective, as described in the section 6 of this document, based on the analysis of humoral immunogenicity results up to six months (Month 20) following last study visit in NTHi-Mcat-001.
  - The analysis of secondary objective, as described in the section 6 of this document, based on safety data collected between last visit in parent study NTHi-Mcat-001 (Month 14) and up to Visit 1 (Month 20).

  This analysis will be performed on cleaned data and will be reviewed internally only. Individual listing will be provided at this stage.

  If the data of the NTHI-MCAT 001 study will not be available and cleaned (freezed), an ANOVA model with only group as independent variable will be fitted instead of the planned ANCOVA model to estimate GMR between groups and placebo.

- The analysis of data up to Visit 2 (Month 26) will be performed in a second step for Interim 2. This analysis will include:
  - The analysis of primary objective, as described in the section 6 of this document, based on the analysis of humoral immunogenicity results up to one year (Month 26) following last study visit in NTHi-Mcat-001 study.
  - The analysis of secondary objective, as described in the section 6 of this document, based on safety data collected between last visit in parent study NTHi-Mcat-001 (Month 14) and up to Visit 2 (Month 26).

  This analysis will be performed on cleaned data and will be reviewed internally only. Individual listing will be provided at this stage.
- The analysis of data up to Visit 4 (Month 38) will be performed in a third step for Interim 3. This analysis will include:
  - The analysis of primary objective, as described in the section 6 of this document, based on the analysis of humoral immunogenicity results up to one year (Month 26) following last study visit in NTHi-Mcat-001 study.
  - The analysis of secondary objective, as described in the section 6 of this document, based on safety data collected between last visit in parent study NTHi-Mcat-001 (Month 14) and up to Visit 4 (Month 38).

  This analysis will be performed on cleaned data and will be reviewed internally only. Individual listing will be provided at this stage.
- The analysis of data up to study end will be performed in a final step for Final Analysis. This analysis will include:
  - The analysis of primary objective, as described in the section 6 of this document, based on immunogenicity results of each study visit.
  - The analysis of secondary objective, as described in the section 6 of this document, based on safety data collected between last visit in parent study NTHi-Mcat-001 (Month 14) and up to study end.

  This analysis will be performed on cleaned data and be documented in a statistical report. Individual listing will be provided at this stage.

9. CHANGES FROM PLANNED ANALYSES

Not Applicable.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The Tables, Figures and Listings (TFL) TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analysis 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 names will be used in the TFLs, to be in line with the T-domains:

Table 3 Groups Labels

Group order in tables	Group label in tables	Group definition for footnote
1	10-10-10-AS	2 doses of AS01E-adjuvanted NTHi/Mcat vaccine containing 10 µg of PD, PE-PilA and UspA2
2	10-10-3-AS	2 doses of AS01E-adjuvanted NTHi/Mcat vaccine containing 10 µg of PD, PE-PilA and 3 µg of UspA2
3	PLACE2	2 doses of saline solution (Step 1 + Step 2)

The following sub-group names will be used in the TFLs

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	50-59 years	50-59 years old subjects
2	60-71years	60-71 years old subjects

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

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

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the Newcombe asymptotic method [method six from Robert G. Newcombe, *Interval estimation for the difference between independent proportions: comparison of eleven methods,* Statist Med. 1998; 17, 873-890].

Concentration greater or equal to a given assay limit of quantification (e.g. 153 EU/ml for anti-PD antibody) is defined as binary variable for non-missing values as:

=1, if concentration is superior or equal to the given assay limit of quantification

=0, otherwise

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,...,t_n are *n* observed immunogenicity concentrations.

Log-transformed immunogenicity values are normally distributed.

GMR measures the changes in immunogenicity concentrations *within* subjects. The GMR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(\gamma_{ij}/\gamma_{ik})}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(\gamma_{ij})-\log_{10}(\gamma_{ik})}{n}\right\}}$$

Where, for n subjects, $\boldsymbol{\gamma_{ij}}$ and $\boldsymbol{\gamma_{ik}}$ are observed immunogenicity concentrations for subject *i* at time-points j and k, j ≠ k.

k: baseline

Duration in the study is defined in days as:

Last visit date (visit x) [a] – Enrolment date (visit Month 20) + 1

[a] or premature discontinuation date (in case of withdrawal from the study). The duration is missing if one of the dates is missing or incomplete.

11.2. Standard data derivation

11.2.1. Date derivation

- Statistical Analysis System (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.
- Duration: Duration of an event is expressed in days. It is the number of days between the start & the stop dates + 1. Therefore, duration is 1 day for an event starting & ending on the same day.
- Association of an event to the primary epoch: An adverse event belongs to the primary epoch, if the onset date is before and excluding Visit 6 or the last contact date, whichever is coming first.

11.2.2. Demography

- Age: Age at the first dose in parent study, computed as the number of units between the date of birth and date of the first dose in parent study. Note that due to incomplete date, the derived age may be incorrect by 1 month when month is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

11.2.3. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- The GMCs calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the assay limit of quantification will be given an arbitrary value of half the assay limit of quantification for the purpose of GMC calculation. The assay limit of quantification value is defined by the laboratory before the analysis and is described in the protocol.
- A seronegative subject is a subject whose antibody concentration is below the assay lower limit of quantification (LLOQ). A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay LLOQ.
- The assay LLOQ value is the value under which there is no quantifiable result available. For an assay with a specific ‘cut_off’ , numerical immuno result is derived from a character field (rawres):
  If rawres is ‘NEG’ or ‘-’ or ‘(-)’, numeric result= cut_off/2,
  if rawres is ‘POS’ or ‘+’ or ‘(+)’, numeric result = cut_off,

if rawres is '< value' and value<=cut_off, numeric result =cut_off/2,
if rawres is '< value' and value>cut_off, numeric result =value,
if rawres is '> value' and value<cut_off, numeric result =cut_off/2,
if rawres is '> value' and value>=cut_off, numeric result =value,
if rawres is '<= value' or '>= value' and value<cut_off, numeric result =cut_off/2,
if rawres is '<= value' or '>= value' and value>=cut_off, numeric result =value,
if rawres is a value < cut_off, numeric result = cut_off/2,
if rawres is a value >= cut_off, numeric result = rawres,
if rawres is a value >= cut_off, numeric result = rawres,
else numeric result is left blank.

11.2.4. Safety

For analysis of SAEs or pIMDs by primary MedDRA term, and for the analysis of concomitant medications, all subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

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 will differ from one table to another.

Event	N used for deriving % per subject
SAEs and pIMDs	All subjects enrolled
Concomitant medication	All subjects enrolled

- Concerning AEs:
  - For the analysis CRDL will perform a review of AEs with respect to the treatment group (i.e., Vaccine received in the parent study).
  - The AEs will be classified:

1. as pIMDs: Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. The investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.In order to facilitate the documentation of pIMDs in the eCRF a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.
2. as SAE: Serious Adverse Event (SAE) is defined in section 8.1.2 of the study protocol.

Number of decimals displayed:

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

Display	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
Immunogenicity	Ratio of GMC	2
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
All summaries	p-value	3