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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	An observer-blind study to evaluate the safety, reactogenicity and immunogenicity of the investigational GSK Biologicals' COPD vaccine (GSK3277511A) in adults.
eTrack study number and Abbreviated Title	207759 (NTHI MCAT-008)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Amendment 1 Final: 09 December 2019
Co-ordinating author:	PPD and PPD
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

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LIST OF ABBREVIATIONS

AE	Adverse event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CTRS	Clinical Trial Registry Summary
eCRF	electronic Case Report Form
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
EU/ml	ELISA unit per millilitre
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PCD	Primary Completion Date
PD	Protocol Deviation
PPS	Per Protocol Set

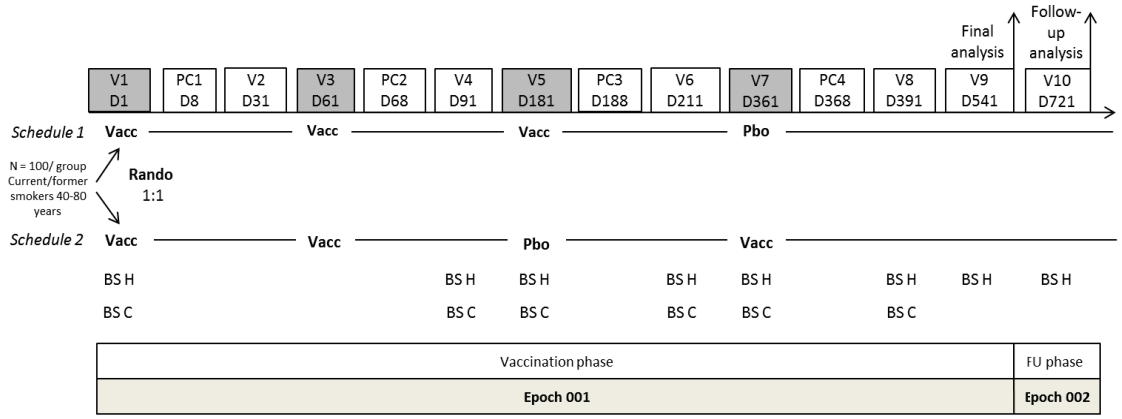
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SHS	Study Headline Summary
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
WBR	Web-based Randomization

1. DOCUMENT HISTORY

Date	Description	Protocol Version
05-MAR-2018	First version	Final – 28-JULY-2017 - v2.0
09-DEC-2019	Amendment 1: to align with protocol amendment 2 and define safety sets	Amendment 2 - 24-JULY-2019 – v2.0

2. STUDY DESIGN

Figure 1 Study design overview



BS H = blood sample for humoral immune responses
BS C = blood sample for cellular immune responses from 20% of subjects in each group
Rando = randomisation; **V** = Visit; **D** = Day; **Vacc** = vaccination (indicated in grey)
Vaccine = 10-10-3-AS formulation; **Pbo** = Placebo; **FU** = Follow-up; **PC** = Phone contact

Experimental design: Phase II, observer-blind, randomised, multi-centric study with two parallel groups.

Duration of the study: for each subject enrolled, the study will last approximately 2 years from Visit 1 (enrolment visit):

- Epoch 001 : Primary (Vaccination phase) starting at Visit 1 (Day 1) and ending at Visit 9 (Day 541).
- Epoch 002 : Long-term follow-up starting after Visit 9 (Day 541) and ending at Visit 10 (Day 721).

Primary Completion Date (PCD): Visit 9 (Day 541).

Refer to the Glossary of terms of the protocol for the definition of PCD.

End of Study (EoS): Last testing results released of samples collected at Visit 10 (Day 721).

Refer to the Glossary of terms of the protocol for the definition of EoS.

Study groups:

- **Schedule 1** : Approximately 100 subjects receiving three doses of the $AS01_E$-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine containing 10 µg of PD, 10 µg of PE-PilA, and 3.3 µg of UspA2 at Visit 1 (Day 1), Visit 3 (Day 61) and Visit 5 (Day 181) and one dose of placebo at Visit 7 (Day 361).
- **Schedule 2 :** Approximately 100 subjects receiving three doses of the $AS01_E$-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine containing 10 µg of PD, 10 µg of PE-PilA, and 3.3 µg of UspA2 at Visit 1 (Day 1), Visit 3 (Day 61) and Visit 7 (Day 361) and one dose of placebo at Visit 5 (Day 181).

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
Schedule 1	100	40 – 80 years	x	x
Schedule 2	100	40 – 80 years	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		Schedule 1	Schedule 2
10-10-3/AS01E	NTHi-Mcat 10-10-3	x	x
	AS01E	x	x
Placebo	Formulation buffer S9b	x	x

Vaccination schedule: at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 7 (Day 361).

Treatment allocation: subjects will be allocated to a study group using a centralised randomisation system on internet (SBIR).

Blinding: observer-blind (Epoch 001) and open (Epoch 002).

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	open

Sampling schedule:

- Blood samples for assessment of humoral immunogenicity will be collected from all subjects at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 211), Visit 7 (Day 361), Visit 8 (Day 391), Visit 9 (Day 541) and Visit 10 (Day 721).
- Blood samples for assessment of cell-mediated immunogenicity (CMI) will be collected from all subjects in the CMI sub-cohort at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 211), Visit 7 (Day 361) and Visit 8 (Day 391).

Type of study: self-contained.

Data collection: Electronic Case Report Form (eCRF), Diary Cards and Phone contacts.

Safety monitoring: on going safety evaluations will be performed by the Safety Review Team (SRT) (blinded). Refer to Section 8.10 of the protocol for description of safety monitoring.

3. OBJECTIVES

3.1. Primary objective

- To evaluate the safety and reactogenicity profile of the NTHi-Mcat vaccine administered according to two vaccination schedules

Refer to Section 4.1 for the definition of the primary endpoints.

3.2. Secondary objectives

- To evaluate the long term safety profile.
- To evaluate the humoral immunogenicity of the NTHi-Mcat investigational vaccine.
- To evaluate the cellular immunogenicity (CD4+ T cell response) of the NTHi-Mcat investigational vaccine.

Refer to Section 4.2 for the definition of the secondary endpoints.

3.3. Tertiary objectives

- To explore the T helper profile to the PD-, PE-, PilA-, UspA2 -specific CD4+/ CD8+ T cell responses.
- To evaluate the cellular immunogenicity (CD8+ T cell response) of the NTHi-Mcat investigational vaccine**.**
- To collect blood samples for assay development/validation and/or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.

4. ENDPOINTS

4.1. Primary endpoints

Safety

Solicited local and general symptoms.

– Occurrence of each solicited local and general symptom (any and Grade 3) reported within 7 days (Day 1 – Day 7) after each vaccination, within each vaccination schedule.

Unsolicited adverse events.

- Occurrence of each unsolicited AE reported within 30 days (Day 1 – Day 30) after any vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, within each vaccination schedule.

Serious adverse events.

- Occurrence of any serious adverse events reported from Day 1 (Visit 1) up to and including Day 541 (Visit 9), within each vaccination schedule.

Potential immune-mediated diseases (pIMDs).

- Occurrence of pIMDs reported from Day 1 (Visit 1) up to and including Day 541 (Visit 9), within each vaccination schedule.

4.2. Secondary endpoints

Long Term Safety

Serious adverse events.

- Occurrence of any serious adverse events reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.

Potential immune-mediated diseases (pIMDs).

- Occurrence of pIMDs reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.

Humoral Immunogenicity

Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations, as measured by ELISA, at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.

Anti-PD, anti-PE, anti-PilA and anti-UspA2 seropositivity, as measured by ELISA, at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.

Refer to Section 6.4.2.1 for the definition of seropositivity.

Cellular Immunogenicity on CD4+ T cells

NTHi-specific and Mcat-specific cell-mediated immune responses as measured by flow cytometry ICS [frequency of specific CD4+ T-cells expressing two or more markers, such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), and CD40 ligand (CD40L)], at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391, in a sub-cohort of subjects and within each vaccination schedule.

4.3. Tertiary endpoints

T Helper profile

T helper profile of the specific CD4+ and CD8+ T cell response based on the expression of T helper 1, T helper 2 and T helper 17 specific markers at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391, within each vaccination schedule.

Cellular Immunogenicity on CD8+ T cells

NTHi-specific and Mcat-specific cell-mediated immune responses as measured by flow cytometry ICS [frequency of specific CD8+ T-cells expressing two or more markers, such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), and CD40 ligand (CD40L)], at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391, in a sub-cohort of subjects and within each vaccination schedule.

5. ANALYSIS SETS

5.1. Definition

The following analysis sets are defined and will be evaluated at the end of the study:

5.1.1. Exposed set

The exposed set (ES) will include all subjects with at least 1 study vaccine administration documented, with respect to the vaccine actually administered:

- A safety analysis will be based on the Exposed, Solicited and Unsolicited Sets:
  - Solicited Set will include all subjects in the exposed set that provided solicited safety data;
  - Unsolicited Set will include all subjects in the exposed set that reported having/not having unsolicited AEs.

5.1.2. Full Analysis Set

The full analysis set (FAS) will include all subjects with at least 1 study vaccine administration for whom immunogenicity data are available:

- An **immunogenicity** analysis based on the FAS will include all vaccinated subjects for whom immunogenicity data are available.

The FAS analysis will be performed per treatment as planned in the randomization.

5.1.3. Per-protocol set for analysis of immunogenicity

The per-protocol set (PPS) for immunogenicity will include all subjects in the FAS:

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule, as specified in Table 6 of the protocol.
- Who received the study vaccines according to protocol procedures.
- Who did not receive a concomitant medication/ product leading to elimination from the PPS analysis (see section 6.6.2 of the protocol) up to 1 month post-Dose 4 visit (Day 391).
- Who did not present an intercurrent medical condition leading to elimination from the PPS analysis for immunogenicity (see section 6.7 of the protocol) up to the 1 month post-Dose 4 visit (Day 391).
- Who complied with the blood sample timings as specified in table 6 of the protocol.
- For whom post-vaccination immunogenicity results are available for at least 1 assay

Note: subjects for whom pre-vaccination immunogenicity results are not available will only be included in the seropositivity analysis.

5.2. Criteria for eliminating data from Analysis Sets

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

5.2.1. Elimination from Exposed Set (ES)

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

A subject will be excluded from the safety 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
1150	No post-vaccination safety data
1160	No solicited safety data

5.2.1.1. Elimination from Solicited Safety Set

Code 1030, code 900 and code 1160 will be used to identify subjects eliminated from the Solicited Safety Set. Code 1070 will be used to identify subjects eliminated from the Solicited Safety Set by visit when vaccination is not administered at that visit.

5.2.1.2. Elimination from Unsolicited Safety Set

Code 1030, code 900 and code 1150 will be used to identify subjects eliminated from the Unsolicited Safety Set.

Code 1150 will be attributed to subjects if all the following conditions are met:

- did not complete the safety assessment following the 7-day follow-up period after each vaccination (i.e. phone contacts),
- did not return any paper Diary after each vaccination,
- did not return for the scheduled visit 30-days after each vaccination,
- did not report any unsolicited AE.

Code 1070 will be used to identify subjects eliminated from the Solicited Safety Set by visit when vaccination is not administered at that visit.

5.2.2. Elimination from Full analysis Set (FAS)

5.2.2.1. Excluded subjects

A subject will be excluded from the FAS 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
2100.a	Serological results not available after all vaccination (for Antibody determination)
2100.b	Serological results not available after all vaccination (for CMI responses)

5.2.3. Elimination from Per-protocol analysis Set (PPS)

5.2.3.1. Excluded subjects

A subject will be excluded from the PPS 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*
1050	Randomization failure
1060	Randomization code was broken
1070	Vaccination not according to protocol
1080	Vaccine temperature deviation
1090	Expired vaccine administered
2010	Protocol violation (inclusion/exclusion criteria)**
2030	Laboratory values outside range before any vaccination (for Antibody determination)
2040	Administration of any medication forbidden by the protocol*
2050	Medical condition forbidden by the protocol
2080	Subjects did not comply with vaccination schedule
2090	Subjects did not comply with blood sample schedule (for Antibody determination)
2100	Serological results not available post-vaccination (for Antibody determination)
2120	Obvious incoherence or abnormality or error in lab data (for Antibody determination)
2130	Subject not planned to be bled for their all blood sampling visits

*See protocol sections 6.6.1 and 6.6.2 for specific details.
**See protocol sections 4.2 and 4.3 for specific details.
*** See Study Procedure Manual for details.

5.2.3.2. Right censored Data

Data from a subject will be censored from visit x for the PPS analysis under the following conditions. The code ****.X+ will also be used to identify study withdrawal from visit x.

Code	Condition under which the code is used
1040.x+	Administration of concomitant vaccine(s) forbidden in the protocol
1060.x+	Randomization code was broken
2040.x+	Administration of any medication forbidden by the protocol

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

The following important protocol deviations will be reported by groups:

- Forced randomization: in case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

- Manual randomization: in case the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule.
- In case unexpected vaccinations at study start were granted due to regulatory recommendation, the subjects who had such vaccination might be mentioned.
- Subjects of childbearing potential without pregnancy test for whom the pregnancy did not happen.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in annex 1 (Section 11).

6.1. Demography

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

Demographic and baseline characteristics such as age at enrolment, sex, race, ethnicity and smoking status will be summarised by study group using descriptive statistics, for the Exposed Set:

- Frequency tables will be generated for categorical variable such as sex, race, ethnicity, age category, smoking status;
- Mean, median, standard deviation, minimum and maximum will be provided for continuous data such as age and pack-years of smoking.

The following variables will be included in demography summary and listings:

- Age in year
- Age category: 40-59 y, 60-80y
- Gender: Male, Female
- Race: (all reported in e-CRF)
- Ethnicity: Hispanic or Latino, Not Hispanic nor Latino
- Pack-years of smoking
- Smoking status

While, additionally, the following vital signs will be tabulated as baseline characteristics:

- Height (cm)
- Weight (kg)
- Body temperature
- Heart rate
- Respiratory rate
- Systolic Blood Pressure
- Diastolic Blood Pressure,

Demographic table will be also presented for All enrolled set, if differs from ES.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per study 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 the different analysis sets will be tabulated.

No inferential analyses of demographic data are planned.

6.1.2. Additional considerations

6.1.2.1. Vaccination and Medical History

The frequencies and percentages of subjects with medical history and by MedDRA body system and preferred term will be presented overall and by vaccine group.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The number of vaccinations the subjects will receive will be tabulated for each study group.

6.3. Efficacy/Effectiveness

6.3.1. Analysis of efficacy planned in the protocol

Not Applicable.

6.3.2. Additional considerations

Not Applicable.

6.4. Immunogenicity

6.4.1. Analysis of immunogenicity planned in the protocol

The analysis will be performed on the PPS at first line. If the percentage of vaccinated subjects with serological results excluded from the PPS is more than 10%, a second line analysis will be performed on the FAS.

The CMI analysis will be performed on the FAS – CMI Subset.

6.4.1.1. Humoral Immunogenicity

6.4.1.1.1. Within groups assessment

ELISA

For each group, eight timepoints (Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, when blood samples are collected) are considered for humoral immune response against the four antigens PD, PE, PilA and UspA2, for which the following will be computed:

- Seropositivity rate and associated 95% CI at each time point (See Additional considerations for seroresponse definition and assay cut-off values).
- GMCs at each time point and their 95% CIs.

With respect to antibody levels at Day 1 (before 1st dose):

- GMRs at each time point and their 95% CIs.
- Percentage of subjects with 2-fold, 4-fold and 8-fold increase at each time point and associated 95% CI.

With respect to antibody levels at Day 181 (before 3rd dose):

- GMRs at Day 211, Day 361, Day 391, Day 541 and Day 721 and their 95% CIs.
- Percentage of subjects with 2-fold, 4-fold and 8-fold increase at Day 211, Day 361, Day 391, Day 541 and Day 721 and associated 95% CI.

With respect to antibody levels at Day 361 (before 4th dose):

- GMRs at Day 391, Day 541 and Day 721 and their 95% CIs.
- Percentage of subjects with 2-fold, 4-fold and 8-fold increase at Day 391, Day 541 and Day 721 and associated 95% CI.

The distribution of antibody concentrations will be displayed using Reverse Cumulative Curves.

6.4.1.1.2. Between groups assessment

Comparative analyses will be exploratory with the aim to characterise the difference between groups in humoral immune response.

At each visit, the group difference in terms of GMCs and GMRs (except at Day 361) will be evaluated, by computing GMC and GMR ratio, between the two groups, and their associated two-sided 95% CIs.

Differences in percentages of subjects with ELISA concentration > 'Assay cut-off' between the groups will be also calculated with the associated two-sided 95% CIs.

6.4.1.2. Cell-mediated immune response

CMI induced by the NTHi-Mcat candidate vaccine will be evaluated presenting the frequencies (including mean, medium, minimum and maximum) of antigen-specific CD4+ /CD8+T cells per 10^6 cells. The specific CD4+/ CD8+T cells being identified as the CD4+/ CD8+ T cells expressing at least 2 different cytokines/activation markers among CD40 Ligand (CD40L), IL-2, TNF-α, IFN- γ, IL-13 and IL-17 upon *in vitro* stimulation will also be evaluated. Descriptive statistics (Min, Q1, Median, Q3 & Max) will be reported for each group at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391.

6.4.1.3. T helper profile

T helper profile of the specific CD4+ and CD8+ T cells response will be evaluated with the frequencies of antigen (stimulation) specific $CD4^+$/ $CD8^+$ T-cells expressing T helper 1, T helper 2 and T helper 17 specific markers (IFN-γ, IL-13 and IL-17 respectively) and will be summarised by means of descriptive statistics (mean, SD, minimum, Q1, median, Q3, and maximum) for each group and at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391.

6.4.2. Additional considerations

6.4.2.1. Humoral Immunogenicity

- Calculation of the GMCs will be performed by taking the anti-logarithm in base 10 (anti-log10) of the mean of the log10 ELISA concentration.
- Antibody concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of geometric mean concentration (GMC) calculation.
- A seronegative subject is defined as a subject whose antibody concentration is below the assay cut-off value (i.e. the ELISA lower limit of quantification). Specifically, the assay cut-off values are defined as follows:

  Anti-PD antibodies: 153 EU/mL

  Anti-PE antibodies: 16 EU/mL

  Anti-PilA antibodies: 8 EU/mL

  Anti-UspA2 antibodies: 28 EU/mL

  Assay cut-off and unit might be subject to change during the study (e.g. in case of assay re-optimization, qualification, (re)validation or standardization). In this case, this will be documented in the clinical study report.
- A seropositive subject is defined as a subject whose antibody concentration is greater than or equal to the assay cut-off value (i.e. the ELISA lower limit of quantification).
- For a given subject and analysis of a given immunogenicity measurement, missing or unevaluable measurements will not be replaced.

- The percentage of seropositive subjects and associated two-sided 95% Clopper-Pearson [1] confidence intervals (CIs) will be computed by vaccine group at each visit.
- The 95% CIs for the difference between the percentages of seropositive subjects will be computed using Miettinen and Nurminen method [2] which has superior performance characteristics when rates are close to 0 or close to 1 and when compared to those formed from the Wald statistic.
- GMCs for each group and their ratios at each post-exposure timepoint will be calculated by fitting an ANCOVA model including the country, age category (40 - 59 years or 60 - 80 years) and smoking status (current or former smokers) as factors and pre-Dose 1 concentration (as covariate).

The SAS statements that will be used to calculate the adjusted GMC will be similar to:

```
PROC glm;
  BY timepoint antibody;
  CLASS country age smoking_status group;
  MODEL logtiter= log_baseline country age smoking_status group;
  LSMEANS group / tdiff stderr cl pdiff;
RUN;
```

In addition, the GMRs for each group and their ratios between study visit (timepoints) and the baseline measure will be calculated by fitting an ANOVA model on the log10 of the titer ratio between a generic visit x and the baseline visit. This model will include the country, age category (40 - 59 years or 60 - 80 years) and smoking status (current or former smokers) as factors.

The SAS statements that will be used to calculate GMRs between timepoints will be similar to:

```
PROC glm;
  BY timepoint antibody;
  CLASS country age smoking_status group;
  MODEL log(titer_visitx/baseline)= country age
smoking_statusgroup;
  LSMEANS group / tdiff stderr cl pdiff;
RUN;
```

The same approach will be used to compute GMRs with respect to the humoral immune response at Day 181 and at day 361: in these cases, baseline refers to, respectively, Day 181 and Day 361 concentration.

GMCs and GMRs will be obtained by exponentiating the estimate of the log-ratio for each group.

6.4.2.2. Cell Mediated Immunity

- The frequency of **antigen-specific** CD4+ or CD8+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines among IFN-γ, IL-2, IL-13, IL-17, TNF-α and/or CD40L, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines upon *in vitro* stimulation in medium only (background condition). For descriptive statistics purposes, differences less or equal to zero (0) are imputed to 1.

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The analysis for safety will be performed on the Exposed Set, Solicited and Unsolicited Safety Sets.

The number and percentage of subjects with at least one **local solicited AE**, with at least one **general solicited AE** and with any solicited AE during the 7-day follow-up period after each vaccination, will be tabulated with exact 95% confidence interval (CI), after each vaccination and overall by study group. The percentage of doses followed by at least one local solicited AE, by at least one general solicited AE and by any solicited AE will be tabulated overall by group with exact 95% CIs. The same computations will be done for Grade 3 solicited AEs.

The number and percentage of subjects reporting each individual solicited local and general AE during the 7-day follow-up period will be tabulated with exact 95% CI after each vaccination, overall by vaccine schedule and by severity. The percentage of doses followed by each individual solicited local and general AE will be tabulated overall by group and by severity with exact 95% CIs.

For fever, additional analyses will be performed by 0.5°C increments.

All the unsolicited adverse events occurring within 30 days after each vaccination, judged either as related or not related to vaccination by the investigator, will be recorded.

The verbatim reports of **unsolicited** 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 percentage of subjects with at least one unsolicited AE during the 30-day follow-up period after any study vaccination will be tabulated with its exact 95% CI for each group and by MedDRA PT. Similar tabulation will be done for the percentage of subjects, with Grade 3 unsolicited symptoms per dose.

The number of subjects who experienced any **pIMD** or any **SAE** from first vaccination up to 12 months post-Dose 4 will be reported.

The number of subjects who experienced any **SAE**, **death**, **pIMD** or **AE leading to study withdrawal**, from first vaccination up to study conclusion, and any **SAE related to study participation of concurrent GSK medication/ vaccination,** during the entire study period, will be reported.

In case of **Pregnancy** during the study, data follow-up and pregnancy outcomes will be described in detail.

The percentage of subjects using **concomitant medication/ product associated with an AE** will be summarised per group for each study vaccination and overall study vaccination.

6.5.2. Additional considerations

6.5.2.1. Exclusion of implausible solicited Adverse Event

Some local and systemic adverse events will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible, therefore these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the Table 4 below:

Table 4 Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Redness	≥ 900 mm < 0 mm
Swelling	For subjects ≥ 6 years: ≥ 500 mm Measurements < 0 mm

6.5.2.2. Solicited Adverse Events

All analyses will be based on the Solicited Safety set.

Solicited adverse events will be reported from Day 1 to Day 7 using structured diaries. The analyses of solicited adverse events will be done based on the interval: Day 1-Day 7.

Temperature (in this study preferred location to measure the temperature is oral cavity or axilla) will be scored at GSK Biologicals as follows:

0: < 37.5°C

1: 37.5-37. 9° C

2: 38.0°C-38.9°C

3: ≥ 39.0°C

In addition, body temperature will be broken down by 0.5 °C increments:

- <36.0,
- 36.0 - 36.4
- 36.5 - 36.9
- 37.0 - 37.4
- 37.5 - 37.9
- 38.0 - 38.4
- 38.5 - 38.9
- 39.0 - 39.4
- 39.5 - 39.9
- ≥40.0°C

Fever, defined as a body temperature of ≥37.5°C irrespective of route of measurement, will be integrated to the summaries as a systemic adverse event.

For the definition of the grading to be reported in the analysis, please refer to Section 6.5.2.2.1 and 6.5.2.2.2.

6.5.2.2.1. Grading definition for Local solicited Adverse Events.

Local AE	Grading	Collection period
Pain at injection site	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - Day 7 after any vaccination
Redness at injection site	0: < 20 mm diameter 1: ≥ 20 mm to ≤ 50 mm diameter 2: > 50 mm to 100 mm diameter 3: > 100 mm diameter	Day 1 - Day 7 after any vaccination
Swelling at injection site	0: < 20 mm diameter 1: ≥ 20 mm to ≤ 50 mm diameter 2: > 50 mm to ≤ 100 mm diameter 3: > 100 mm diameter	Day 1 - Day 7 after any vaccination

6.5.2.2.2. Grading definition for General solicited Adverse Events.

General AE	Grading	Collection period
Headache	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - Day 7 after any vaccination
Fatigue	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - Day 7 after any vaccination
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - Day 7 after any vaccination
Myalgia	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - Day 7 after any vaccination
Chills	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - Day 7 after any vaccination
Fever	0: < 37.5°C 1: 37.5°C to 37.9°C 2: 38.0°C to 38.9°C 3: ≥ 39.0°C	Day 1 - Day 7 after any vaccination

6.5.2.3. Unsolicited Adverse Events

All analyses will be based on the Exposed and Unsolicited Safety set.

All the unsolicited adverse events occurring during the study, judged either as related or not related to vaccination by the investigator, will be recorded. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The unsolicited adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. Adverse events judged by the investigator as related to study vaccine will be summarized by vaccine group, according to system organ class and preferred term within system organ class. When an unsolicited adverse event occurs more than once for a subject, the maximal severity will be counted.

Only vaccine-emergent adverse events will be analysed, i.e., excluding those after a subject has given informed consent but before first vaccination. The selection of unsolicited adverse events and the assignment to time intervals will be done by day of onset and not by days ongoing/persisting.

The analysis of unsolicited adverse events is summarised according to the following categories:

After any and each vaccination

- Unsolicited adverse events with onset within 30 days after vaccination
- Related unsolicited adverse events with onset within 30 days after vaccination
- Grade 3 unsolicited adverse events with onset within 30 days after vaccination
- Grade 3 related unsolicited adverse events with onset within 30 days after vaccination

By Epoch and overall

- Serious unsolicited adverse events
- Related serious unsolicited adverse events
- Potential immune-mediated diseases (pIMDs)
- Fatal unsolicited adverse events
- Related fatal unsolicited adverse events
- Unsolicited adverse events leading to hospitalization
- Unsolicited adverse events leading to premature withdrawal from study

6.5.2.4. Combined Solicited and Unsolicited Adverse Events

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	Preferred term code	Corresponding Preferred term decode
Pain	10022086	Injection site pain
Redness	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Myalgia	10028411	Myalgia
Chills	10008531	Chills
Fever	10016558	Pyrexia

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.

6.5.2.5. Clinical Safety Laboratory Investigations

Not Applicable.

6.5.2.6. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects reporting concomitant medications will be tabulated by vaccine group for each study dose and across doses. The following concomitant medication categories will be considered in the summaries

- All concomitant vaccines or medications or products, associated with an AE, except vitamins and dietary supplements, administered during the entire study period following the first dose of study vaccine (Day 1 to Day 721).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring.
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

7. ANALYSIS INTERPRETATION

All safety and immunogenicity analyses are planned with the intention to estimate the safety and immune response after a third injection.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS)requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final Analysis epoch 1	E1_01	SR	Y	Y	See references TFL TOC
Follow-up epoch analysis	E1_02	SR	Y		Y

8.2. Statistical considerations for interim analyses

No interim analysis is planned for this study. Data up to and including Day 541 (i.e. Visit 9) are considered 'final' and completed data, while the remaining 6 months open label safety data are considered long-term safety follow-up.

9. CHANGES FROM PLANNED ANALYSES

Not Applicable.

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 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:

Group order in tables	Group label in tables	T-domains	Group definition for footnote
1	Schedule 0-2-6	Schedule 1	Third dose at six months.
2	Schedule 0-2-12	Schedule 2	Third dose at one year.

The group names in the Protocol, Schedule 1 and Schedule 2, will be renamed as Schedule 0-2-6 and Schedule 0-2-12, respectively, in all the statistical analyses and in the study report.

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

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

2. Miettinen O and Nurminen M. “Comparative analysis of two rates.” *Statistics in Medicine* 1985; 4:213-226

11.2. Standard data derivation

GSK legacy

11.2.1. Date derivation

- SAS date derived from a character date: in case day is missing, [1]5 is used. In case day & month are missing, 30 June 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 including Visit 9 or the last contact date, whichever is coming first.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 1 refers to all vaccines administered at the first vaccination visit while dose 2 corresponds to all vaccinations administered at the second vaccination visit even if this is the first time a product is administered to the subject.
- 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. In case a study dose is not administered and an event occurs after the subsequent study dose (e.g. 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g. dose 3).
- The number of doses for a product is the number of time the product was administered to a subject.
- The incidence per dose is the number of vaccination visits at which an event was reported among all vaccination visits.

11.2.3. Demography

- Age: age at the enrolment, computed as the number of units between the date of birth and the enrolment. Note that due to incomplete date, the derived age may be incorrect; this may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.
- Conversion of weight to kg

  The following conversion rule is used:

  - Weight in Kilogram= weight in Pounds / 2.2
  - Weight in Kilogram =weight in ounces / 35.2

  The result is rounded to 2 decimals.

- Conversion of height to cm

  The following conversion rule is used:

  - Height in Centimetres = Height in Feet * 30.48
  - Height in Centimetres = Height in Inch * 2.54

  The result is rounded to the unit (i.e. no decimal).

- Conversion of temperature to °C

  The following conversion rule is used:

  - Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The result is rounded to 1 decimal.

- Smoking status conversion

  Subjects reporting smoking status START DATE='Before' and STOP DATE='Before' will have value 'Former' (i.e., no smoker)

  Subjects reporting smoking status START DATE='Before' and STOP DATE='Ongoing' will have value 'Current' (i.e., smoker)

11.2.4. 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 Geometric Mean Concentrations (GMC) calculations are performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. Antibody concentration above the assay cut-off (i.e. the ELISA upper limit of quantification) will be given twice the cut-off value.
- A seronegative subject is a subject whose antibody concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody concentration is greater than or equal to the cut-off value of the assay.
- All CIs computed will be two-sided 95% CIs.

11.2.5. Safety

Solicited adverse event: with the exception of 60 minutes after vaccination, solicited adverse events are collected via paper-diary and thus no DCF (data clarification form) will apply in case of inconsistency reporting.

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Solicited Safety Set will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose;
- subjects who reported solicited safety data at a visit, but they didn't report any daily measurement for a certain symptom, they will be counted as missing for that symptom at that visit;
- subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period;
- doses without symptom sheets documented will be excluded;
- the duration of solicited adverse events will be calculated as the sum of the consecutive days with the symptom reported at Grade 1 or higher. The duration of solicited events at a specific grade (e.g., Grade 3) will be calculated as the sum of the consecutive days with the symptom reported at that grade. The same rule applies for solicited adverse events ongoing at the end of the solicited follow-up period considering the maximum intensity reported;
- when the occurrences of solicited adverse events are summarised, each event recorded as having occurred during a specific period will be counted as the number of occurrences the event is consecutively reported (at Grade 1 or higher);
- when the occurrences of solicited adverse events at a specific grade are summarised, each event recorded as having occurred at that grade during a specific period will be counted as the number of occurrences the event is consecutively reported at that grade.

For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively. 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 for Vaccination phase	N used for deriving % per dose for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered	
Solicited local/ general symptom	All subjects, with study vaccine administered, with at least one solicited symptom, either local or general, documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited symptom, either local or general, documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom with onset within 30 days	All subjects, with study vaccine administered, that have safety data	
Unsolicited symptom (e.g.,SAEs, AEs leading to withdrawal,..)	All subjects with study vaccine administered	
Concomitant medication	All subjects with study vaccine administered	

Potential immune mediated diseases (pIMD).

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.

12. ANNEX 2: 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	Ratio of GMT/C	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

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

A customized mock catalogue will be drafted before the Database Freeze. Until the customized catalogue will not be available, the standard CDISC-SDTM mock TFL will be used as a reference for the TFL TOC tables.

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	An observer-blind study to evaluate the safety, reactogenicity and immunogenicity of the investigational GSK Biologicals' COPD vaccine (GSK3277511A) in adults.
eTrack study number and Abbreviated Title	207759 (NTHI MCAT-008)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 05 March 2018
Co-ordinating author:	PPD
Reviewed by:	PPD (Clinical and Epidemiological Project Leader) PPD (Clinical Research & Development Lead) PPD (Lead Statistician) PPD (Lead Statistical Analyst) PPD (Scientific Writer) PPD (Regulatory Affairs Representative) PPD (SERM physician) PPD (Public Disclosure Representative) PPD (Statistical Peer Reviewer)
Approved by:	PPD (Clinical and Epidemiological Project Leader) PPD (Lead Statistician) 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 ABBREVIATIONS

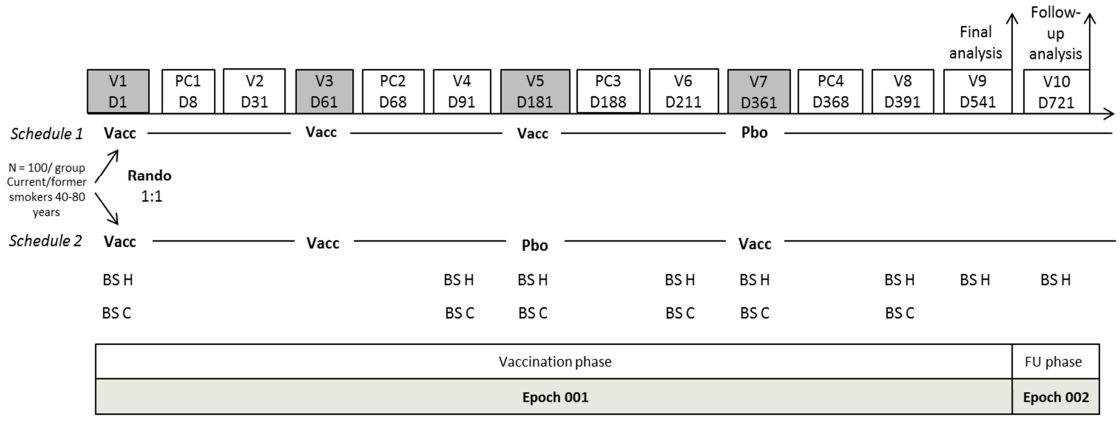
AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EL.U/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PCD	Primary Completion Date
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
WBR	Web-based Randomization

1. DOCUMENT HISTORY

Date	Description	Protocol Version
05-MAR-2018	Final version	Final – 28-JULY-2017

2. STUDY DESIGN

Figure 1 Study design overview



BS H = blood sample for humoral immune responses
BS C = blood sample for cellular immune responses from 20% of subjects in each group
Rando = randomisation; **V** = Visit; **D** = Day; **Vacc** = vaccination (indicated in grey)
Vaccine = 10-10-3-AS formulation; **Pbo** = Placebo; **FU** = Follow-up; **PC** = Phone contact

- **Experimental design:** Phase II, observer-blind, randomised, multi-centric study with two parallel groups.
- **Duration of the study:** for each subject enrolled, the study will last approximately 2 years from Visit 1 (enrolment visit):
  - Epoch 001 : Primary (Vaccination phase) starting at Visit 1 (Day 1) and ending at Visit 9 (Day 541).
  - Epoch 002 : Long-term follow-up starting after Visit 9 (Day 541) and ending at Visit 10 (Day 721).
- Primary Completion Date (PCD): Visit 9 (Day 541).

Refer to the Glossary of terms of the protocol for the definition of PCD.

- **End of Study (EoS):** Last testing results released of samples collected at Visit 10 (Day 721).

Refer to the Glossary of terms of the protocol for the definition of EoS.

- Study groups:
  - **Schedule 1** : Approximately 100 subjects receiving three doses of the $AS01_E$-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine containing 10 µg of PD, 10 µg of PE-PilA, and 3.3 µg of UspA2 at Visit 1 (Day 1), Visit 3 (Day 61) and Visit 5 (Day 181) and one dose of placebo at Visit 7 (Day 361).
  - **Schedule 2 :** Approximately 100 subjects receiving three doses of the $AS01_E$-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine containing 10 µg of PD, 10 µg of PE-PilA, and 3.3 µg of UspA2 at Visit 1 (Day 1), Visit 3 (Day 61) and Visit 7 (Day 361) and one dose of placebo at Visit 5 (Day 181).

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
Schedule 1	100	40 – 80 years	x	x
Schedule 2	100	40 – 80 years	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		Schedule 1	Schedule 2
10-10-3/AS01E	NTHi-Mcat 10-10-3	x	x
	AS01E	x	x
Placebo	Formulation buffer S9b	x	x

- **Vaccination schedule:** at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 7 (Day 361).
- **Treatment allocation:** Subjects will be allocated to a study group using a centralised randomisation system on internet (SBIR).
- **Blinding:** observer-blind (Epoch 001) and open (Epoch 002).

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	open

- **Sampling schedule:**
  - Blood samples for assessment of humoral immunogenicity will be collected from all subjects at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 211), Visit 7 (Day 361), Visit 8 (Day 391), Visit 9 (Day 541) and Visit 10 (Day 721).
  - Blood samples for assessment of cell-mediated immunogenicity (CMI) will be collected from all subjects in the CMI sub-cohort at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 211), Visit 7 (Day 361) and Visit 8 (Day 391).
- **Type of study: self-contained.**

- **Data collection:** Electronic Case Report Form (eCRF), Diary Cards and Phone contacts.
- **Safety monitoring:** On going safety evaluations will be performed by the Safety Review Team (SRT) (blinded). Refer to Section 8.10 of the protocol for description of safety monitoring.

3. OBJECTIVES

3.1. Primary objective

- To evaluate the safety and reactogenicity profile of the NTHi-Mcat vaccine administered according to two vaccination schedules

Refer to Section 4.1 for the definition of the primary endpoints.

3.2. Secondary objectives

- To evaluate the long term safety profile.
- To evaluate the humoral immunogenicity of the NTHi-Mcat investigational vaccine.
- To evaluate the cellular immunogenicity of the NTHi-Mcat investigational vaccine.

Refer to Section 4.2 for the definition of the secondary endpoints.

3.3. Tertiary objectives

- To explore the T helper profile of the PD-, PE-, PilA-, UspA2-specific CD4+/ CD8+ T cell responses.
- To collect blood samples for assay development/validation and/or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.

4. ENDPOINTS

4.1. Primary endpoints

Safety

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) reported within 7 days (Day 1 – Day 7) after each vaccination, within each vaccination schedule.
- Unsolicited adverse events.
  - Occurrence of each unsolicited AE reported within 30 days (Day 1 – Day 30) after any vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, within each vaccination schedule.

- Serious adverse events.
  - Occurrence of any serious adverse events reported from Day 1 (Visit 1) up to and including Day 541 (Visit 9), within each vaccination schedule.
- Potential Immune-mediated diseases (pIMDs).
  - Occurrence of pIMDs reported from Day 1 (Visit 1) up to and including Day 541 (Visit 9), within each vaccination schedule.

4.2. Secondary endpoints

Long Term Safety

- Serious Adverse events
  - Occurrence of any serious adverse events reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.
- Potential Immune-mediated diseases (pIMDs).
  - Occurrence of pIMDs reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.

Humoral Immunogenicity

- Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations, as measured by ELISA, at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.
- Anti-PD, anti-PE, anti-PilA and anti-UspA2 seropositivity, as measured by ELISA, at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.

Cellular Immunogenicity

- NTHi-specific and Mcat-specific cell-mediated immune responses as measured by flow cytometry ICS (frequency of specific CD4+/CD8+ T-cells expressing two or more markers, such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), and CD40 ligand (CD40L), at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391, in a sub-cohort of subjects and within each vaccination schedule.

4.3. Tertiary endpoint

T Helper profile:

- T helper profile of the specific CD4+ (CD8+) T cell response based on the expression of T helper 1, T helper 2 and T helper 17 specific markers at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391, within each vaccination schedule.

5. ANALYSIS SETS

5.1. Definition

The following analysis sets are defined and will be evaluated at the end of the study:

5.1.1. Exposed set

The exposed set (ES) will include all subjects with at least 1 study vaccine administration documented, with respect to the vaccine actually administered:

- A **safety** analysis based on the ES will include all subjects with at least one vaccine dose administered and who provided safety data.

5.1.2. Full Analysis Set

The full analysis set (FAS) will include all subjects with at least 1 study vaccine administration for whom immunogenicity data are available:

- An **immunogenicity** analysis based on the FAS will include all vaccinated subjects for whom immunogenicity data are available.

The FAS analysis will be performed per treatment as planned in the randomization.

5.1.3. Per-protocol set for analysis of immunogenicity

The per-protocol set (PPS) for immunogenicity will include all subjects in the FAS:

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule, as specified in Table 10 of the protocol.
- Who received the study vaccines according to protocol procedures.
- Who did not receive a concomitant medication/ product leading to elimination from the PPS (per-protocol) analysis see section 6.6.2 of the protocol) up to the 1 month post-Dose 4 visit (Day 391).
- Who did not present an intercurrent medical condition leading to elimination from the PPS analysis for immunogenicity (see section 6.7 of the protocol) up to the 1 month post-Dose 4 visit (Day 391).
- Who complied with the blood sample timings as specified in table 10 of the protocol.
- For whom post-vaccination immunogenicity results are available for at least 1 assay at each immunogenicity assessment timepoint.

5.2. Criteria for eliminating data from Analysis Sets

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

5.2.1. Elimination from Exposed Set (ES)

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 ES

5.2.2. Elimination from Full analysis Set (FAS)

5.2.2.1. Excluded subjects

A subject will be excluded from the FAS 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
2100	Serological results not available after all vaccination.

5.2.3. Elimination from Per-protocol analysis Set (PPS)

5.2.3.1. Excluded subjects

A subject will be excluded from the PPS 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*
1050	Randomization failure
1060	Randomization code was broken
1070	Subjects got vaccinated with the correct vaccine but containing a lower volume
1070	Vaccination not according to protocol
1080	Vaccine temperature deviation
1090	Expired vaccine administered
2010	Protocol violation (inclusion/exclusion criteria)**
2020	Initially unknown antibody status
2030.a	Laboratory values outside range before any vaccination (for Antibody determination)***
2030.b	Laboratory values outside range before any vaccination (for CMI responses)***
2040	Administration of any medication forbidden by the protocol*
2080	Subjects did not comply with vaccination schedule
2090	Subjects did not comply with blood sample schedule
2100	Serological results not available post-vaccination
2110	Blood sample available but not yet tested (interim analysis)
2120.a	Obvious incoherence or abnormality or error in lab data (for Antibody determination)
2120.b	Obvious incoherence or abnormality or error in lab data (for CMI responses)
2130	Subject not planned to be bled for their all blood sampling visits

*See protocol sections 6.6.1 and 6.6.2 for specific details.
**See protocol sections 4.2 and 4.3 for specific details.
*** See Study Procedure Manual for details.

5.2.3.2. Right censored Data

Data from a subject will be censored from visit x for the PPS analysis under the following conditions. The code ****.X+ will also be used to identify study withdrawal from visit x.

Code	Condition under which the code is used
1040.x+	Administration of concomitant vaccine(s) forbidden in the protocol
1060.x+	Randomization code was broken
2040.x+	Administration of any medication forbidden by the protocol

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

The following important protocol deviations will be reported by groups:

- Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.
- Manual randomization: In case the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule.
- In case unexpected vaccinations at study start were granted due to regulatory recommendation, the subjects who had such vaccination might be mentioned.
- Subjects of childbearing potential without pregnancy test for whom the pregnancy did not happen.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat 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 such as age at enrolment, sex, race, ethnicity and smoking status will be summarised by study group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as sex, race, ethnicity, age category, smoking status;

- Mean, median, standard deviation, minimum and maximum 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 study 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 PPS and FAS will be tabulated.

No inferential analyses of demographic data are planned.

6.1.2. Additional considerations

Not Applicable.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

None.

6.2.2. Additional considerations

The number of vaccinations the subjects will receive will be tabulated for each study group.

6.3. Efficacy/Effectiveness

6.3.1. Analysis of efficacy planned in the protocol

Not Applicable.

6.3.2. Additional considerations

Not Applicable.

6.4. Immunogenicity

6.4.1. Analysis of immunogenicity planned in the protocol

The analysis will be performed on the PPS at first line. If the percentage of vaccinated subjects with serological results excluded from the PPS is more than 10%, a second line analysis will be performed on the FAS.

6.4.1.1. Humoral Immunogenicity

6.4.1.1.1. Within groups assessment

For each group and at each timepoint during which blood samples are collected for humoral immune response (at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721), and for each component (PD, PE, PilA and UspA2), the following will be computed:

- Seropositivity rate and associated 95% CI (See Additional considerations for seroresponse definition and assay cut-off values).
- GMCs and their 95% CIs.
- Percentage of subjects with fold increase including 2-fold, 4-fold and 8-fold increase from baseline and associated 95% CI.

The distribution of antibody concentrations will be displayed using Reverse Cumulative Curves.

6.4.1.2. Cell-mediated immune response

CMI induced by the NTHi-Mcat candidate vaccine will be evaluated, presenting the frequencies (including mean, medium, minimum and maximum) of antigen-specific CD4+ /CD8+T cells per 10^6 cells. The specific CD4+/ CD8+T cells being identified as the CD4+/ CD8+ T cells expressing at least 2 different cytokines/activation markers among CD40 Ligand (CD40L), IL-2, TNF-α, IFN- γ, IL-13 and IL-17 upon *in vitro* stimulation will also be evaluated. A descriptive statistics (Min, Q1, Median, Q3 & Max) will be reported for each group at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391.

6.4.2. Additional considerations

6.4.2.1. Humoral Immunogenicity

- Calculation of the GMCs will be performed by taking the anti-logarithm in base 10 (anti-log10) of the mean of the log10 ELISA concentration.
- Antibody concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of geometric mean concentration (GMC) calculation.

- A seronegative subject is defined as a subject whose antibody concentration is below the assay cut-off value (i.e. the ELISA lower limit of quantification). Specifically, the assay cut-off values are defined as follows:
  - *Anti-PD antibodies: 153 EU/mL*
  - *Anti-PE antibodies: 8 EU/mL*
  - *Anti-PilA antibodies: 7 EU/mL*
  - *Anti-UspA2 antibodies: 18 EU/mL*

Assay cut-off and unit might be subject to change during the course of the study (e.g. in case of assay re-optimization, qualification, (re)validation or standardization). In this case, this will be documented in the clinical study report.

- A seropositive subject is defined as a subject whose antibody concentration is greater than or equal to the assay cut-off value (i.e. the ELISA lower limit of quantification).
- For a given subject and the analysis of a given immunogenicity measurement, missing or unevaluable measurements will not be replaced.
- The percentage of seropositive subjects and associated two-sided 95% Clopper-Pearson confidence intervals (CIs) will be computed by vaccine group at each visit.
- GMCs at each post-exposure timepoint and for each group will be calculated by fitting an ANCOVA model including the country, age category (40 - 59 years or 60 - 80 years) and smoking status (current or former smokers) as factors and pre-Dose 1 concentration (as covariate).

The SAS statements that will be used to calculate the adjusted GMC will be similar to:

```
PROC glm;
  BY timepoint group;
  CLASS country age smoking_status;
  MODEL logtiter= baseline country age smoking_status;
  LSMEANS group / tdiff stderr cl pdiff;
RUN;
```

In addition, the Geometric Mean Ratios (GMR) between study visit (timepoints) and baseline measure will be calculated, for each group, by fitting an ANOVA model on the log10 of the titer ratio between a generic visit x and the baseline visit. This model will include the country, age category (40 - 59 years or 60 - 80 years) and smoking status (current or former smokers) as factors.

The SAS statements that will be used to calculate GMRs between timepoints will be similar to:

```
PROC glm;
  BY timepoint group;
  CLASS country age smoking_status;
  MODEL log(titer_visitx/baseline)= country age smoking_status;
  LSMEANS group / tdiff stderr cl pdiff;
RUN;
```

GMC and GMRs will be obtained by exponentiating the estimate of the log-ratio for each group.

6.4.2.2. Cell Mediated Immunity

- The frequency of **antigen-specific** CD4+ or CD8+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines among IFN-γ, IL-2, IL-13, IL-17, TNF-α and/or CD40L, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines upon *in vitro* stimulation in medium only (background condition). For descriptive statistics purposes, differences less or equal to zero (0) are imputed to 1.

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The analysis for safety will be performed on the ES.

The number and percentage of subjects with at least one **local solicited AE**, with at least one **general solicited AE** and with any solicited AE during the 7-day follow-up period after each vaccination, will be tabulated with exact 95% confidence interval (CI), after each vaccination and overall by study group. The percentage of doses followed by at least one local solicited AE, by at least one general solicited AE and by any solicited AE will be tabulated overall by group with exact 95% CIs. The same computations will be done for Grade 3 solicited AEs.

The number and percentage of subjects reporting each individual solicited local and general AE during the 7-day follow-up period will be tabulated with exact 95% CI after each vaccination and overall by vaccine schedule. The percentage of doses followed by each individual solicited local and general AE will be tabulated overall by group with exact 95% CIs.

The same tabulation will be performed for Grade 3 AEs.

For fever, additional analyses will be performed by 0.5°C increments.

All the unsolicited adverse events occurring within 30 days after each vaccination, judged either as probably related, possibly related, or not related to vaccination by the investigator, will be recorded.

The verbatim reports of **unsolicited** 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 percentage of subjects with at least one unsolicited AE during the 30-day follow-up period after any study vaccination will be tabulated with its exact 95% CI for each group and by MedDRA PT. Similar tabulation will be done for the percentage of doses, for Grade 3 unsolicited symptoms.

The number of subjects who experienced any **pIMD** or any **SAE** from first vaccination up to 12 months post-Dose 4 will be reported.

The number of subjects who experienced any **SAE**, **death**, **pIMD** or **AE leading to study withdrawal**, from first vaccination up to study conclusion, and any **SAE related to study participation of concurrent GSK medication/ vaccination,** during the entire study period, will be reported.

In case of **Pregnancy** during the study, data follow-up and pregnancy outcomes will be described in detail.

The percentage of subjects using **concomitant medication/ product associated with an AE** will be summarised per group for each study vaccination and overall study vaccination.

6.5.2. Additional considerations

6.5.2.1. Exclusion of implausible solicited Adverse Event

Some local and systemic adverse events will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible. Therefore these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the Table 4 below:

Table 4 Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Redness	≥ 900 mm < 0 mm
Swelling	For subjects ≥ 6 years: ≥ 500 mm Measurements < 0 mm

6.5.2.2. Solicited Adverse Events

All analyses will be based on the All Exposed set analysis set.

Solicited adverse events will be reported from day 1 and then until day 7 using structured diaries. The analyses of solicited adverse events will be done based on the interval: Day 1-day 7.

Temperature (in this study preferred location to measure the temperature is oral cavity or axilla) will be scored at GSK Biologicals as follows:

0 : < 37.5°C

1 : 37.5-37. 9° C

2 : 38.0°C-38.9°C

3 : ≥ 39.0°C

The intensity of each AE and SAE should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. Such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2 of the protocol.

Body temperature, in addition, will also be broken down by route of measurement according to the scheme described below:

- by 0.5 °C increments:
  - <36.0,
  - 36.0 - 36.4
  - 36.5 - 36.9
  - 37.0 - 37.4
  - 37.5 - 37.9
  - 38.0 - 38.4
  - 38.5 - 38.9
  - 39.0 - 39.4
  - 39.5 - 39.9
  - ≥40.0°C

Fever, defined as a body temperature of ≥37.5°C irrespective of route of measurement, will be integrated to the summaries as a systemic adverse event.

For the definition of the grading to be reported in the analysis, please refer to Section 6.5.2.2.1 and 6.5.2.2.2.

6.5.2.2.1. Grading definition for Local solicited Adverse Events.

Local AE	Grading	Collection period
Pain at injection site	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - day 7 after any vaccination
Redness at injection site	0 : < 20 mm diameter 1 : ≥ 20 mm to ≤ 50 mm diameter 2 : > 50 mm to ≤ 100 mm diameter 3 : > 100 mm diameter	Day 1 - day 7 after any vaccination
Swelling at injection site	0 : < 20 mm diameter 1 : ≥ 20 mm to ≤ 50 mm diameter 2 : > 50 mm to ≤ 100 mm diameter 3 : > 100 mm diameter	Day 1 - day 7 after any vaccination

6.5.2.2.2. Grading definition for Local solicited Adverse Events.

General AE	Grading	Collection period
Headache	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - day 7 after any vaccination
Fatigue	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - day 7 after any vaccination
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - day 7 after any vaccination
Myalgia	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - day 7 after any vaccination
Chills	0: None 1: Mild 2: Moderate 3: Severe	Day 1 - day 7 after any vaccination
Fever	0 : < 37.5°C 1 : 37.5°C to 37.9°C 2 : 38.0°C to 38.9°C 3 : ≥ 39.0°C	Day 1 - day 7 after any vaccination

6.5.2.3. Unsolicited Adverse Events

All the unsolicited adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, will be recorded. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The unsolicited adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. Adverse events judged by the investigator as at least possibly related to study vaccine will be summarized by vaccine group, according to system organ class and preferred term within system organ class. When an unsolicited adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Only vaccine-emergent adverse events will be analyzed, i.e., excluding those after a subject has given informed consent but before first vaccination. The selection of unsolicited adverse events and the assignment to time intervals will be done by day of onset and not by days ongoing/persisting.

The summaries will also be presented by period of onset and will include frequency distributions of the different adverse events:

- Onset between Vaccination 1 and Vaccination 2.
- Onset between Vaccination 2 and Vaccination 3
- Onset after Vaccination 3

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited adverse event.
- Possibly or probably related unsolicited adverse events.
- Unsolicited adverse events leading to death.
- Serious adverse events.
- Possibly or probably related serious adverse event.
- Unsolicited adverse events leading to premature withdrawal from study.
- Unsolicited adverse events leading to dose reduction, interruption or delay in study vaccination.
- Unsolicited adverse events leading to hospitalization.
- Unsolicited adverse events of special interest.
- Medically attended adverse events.

6.5.2.4. Combined Solicited and Unsolicited Adverse Events

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
Pain	10022086	Pain at injection site
Redness	10022098	Redness at injection site
Swelling	10053425	Swelling at injection site
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Myalgia	10028411	Myalgia
Chills	10008531	Chills
Fever	10016558	Fever

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.

6.5.2.5. Clinical Safety Laboratory Investigations

Not Applicable.

6.5.2.6. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects reporting concomitant medications within will be tabulated by vaccine group for each study dose and across doses. The following concomitant medications category will be considered in the summaries

- All concomitant vaccines or medications or products, associated with an AE, except vitamins and dietary supplements, administered during the entire study period following the first dose of study vaccine (Day 1 to Day 721).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.
- Any concomitant medications/products/vaccines listed in Protocol Section 6.6.2
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

7. ANALYSIS INTERPRETATION

All safety and immunogenicity analyses are planned with the intention to estimate the safety and immune response after a third injection. No comparisons are planned for this study.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS)requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final Analysis epoch 1	E1_01	SR	Y	Y	See references TFL TOC
Follow-up epoch analysis	E1_02	SR	Y		Y

8.2. Statistical considerations for interim analyses

No interim analysis is planned for this study. Data up to and including Day 541 (i.e. Visit 9) are considered 'final' and completed data, while the remaining 6 months open label safety data are considered long-term safety follow-up.

9. CHANGES FROM PLANNED ANALYSES

Not Applicable.

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 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:

Group order in tables	Group label in tables	Group definition for footnote
1	Schedule 1	Third dose at six months.
2	Schedule 2	Third dose at one year.

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

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

Miettinen O and Nurminen M. "Comparative analysis of two rates." *Statistics in Medicine* 1985; 4:213-226

11.2. Standard data derivation

GSK legacy

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.
- 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 including Visit 9 or the last contact date, whichever is coming first.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 1 refers to all vaccines administered at the first vaccination visit while dose 2 corresponds to all vaccinations administered at the second vaccination visit even if this is the first time a product is administered to the subject.
- 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. In case a study dose is not administered and an event occurs after the subsequent study dose (eg 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (eg dose 3).
- The number of doses for a product is the number of time the product was administered to a subject.
- The incidence per dose is the number of vaccination visits at which an event was reported among all vaccination visits.

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. 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.
- Conversion of weight to kg

  The following conversion rule is used:

  - Weight in Kilogram= weight in Pounds / 2.2
  - Weight in Kilogram =weight in oncs / 35.2

  The result is rounded to 2 decimals.
- Conversion of height to cm

  The following conversion rule is used:

  - Height in Centimetres = Height in Feet * 30.48
  - Height in Centimetres = Height in Inch * 2.54

  The result is rounded to the unit (i.e. no decimal).

- Conversion of temperature to °C

  The following conversion rule is used:

  – Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The result is rounded to 1 decimal.

- Smoking status conversion

  Subjects reporting smoking status START DATE='Before' and STOP DATE='Before' will have value 'Former' (i.e., no smoker)

  Subjects reporting smoking status START DATE='Before' and STOP DATE='Ongoing' will have value 'Current' (i.e., smoker)

11.2.4. 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.
- A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay.
- The assay cut-off 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= cutt_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.
- All CI computed will be two-sided 95% CI.

11.2.5. Safety

Solicited adverse event: With the exception of 60 minutes after vaccination, solicited adverse events are collected via e-diary and thus no DCF (data clarification form) will apply in case of inconsistency reporting.

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the All Exposed set will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.

For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively. 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 for Vaccination phase	N used for deriving % per dose for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered	All study visits with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and 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)	All study visits with study vaccine administered and 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	All study visits with study vaccine administered
Concomitant medication	All subjects with study vaccine administered	All study visits with study vaccine administered

Potential immune mediated diseases (pIMD).
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.

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	Ratio of GMT/C	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

12. ANNEX 3: STUDY SPECIFIC MOCK TFL

A customized mock catalogue will be drafted before the Database Freeze. Until the customized catalogue will not be available, the standard CDISC-SDTM mock TFL will be used as a reference for the TFL TOC tables.

This mock catalogue will be uploaded in CARS together with the SAP and the TFL TOC before FSFV.