GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase IIB, randomised, observer-blind, placebo-controlled, multi-centre study to evaluate the efficacy, safety, reactogenicity and immunogenicity of the GSK Biologicals' investigational vaccine GSK3277511A when administered intramuscularly according to a 0, 2 months schedule in COPD patients aged 40 to 80 years with a previous history of acute exacerbation (AECOPD).
eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002) An observer-blind study to evaluate the efficacy, safety, reactogenicity and immunogenicity of the GSK Biologicals' investigational vaccine GSK3277511A when administered to COPD patients
Scope:	All analyses for the final clinical study report
Date of Statistical Analysis Plan	Amendment 1 FDA Draft Final: 13 February 2018 Amendment 2 FDA Draft Final: 29 November 2019
Co-ordinating author:	PPD (Lead Statistician) PPD (Study Statistician)
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

CONFIDENTIAL

207489 (NTHI MCAT-002)
Statistical Analysis Plan Amendment 2 FDA Final Draft

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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
ATP	According to Protocol
CI	Confidence Interval
BMI	Body Mass Index
CMI	Cell-mediated immunogenicity
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CSR	Clinical Study Report
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
EXACT-PRO	EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
HCU	Healthcare utilisation
HRQOL	Health-related quality of life
ICS	Intracellular cytokine staining
iSRC	Internal Safety Review Committee
ITT	Intent to treat
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of quantification
LOD	Limit of detection
ULOQ	Upper limit of quantification

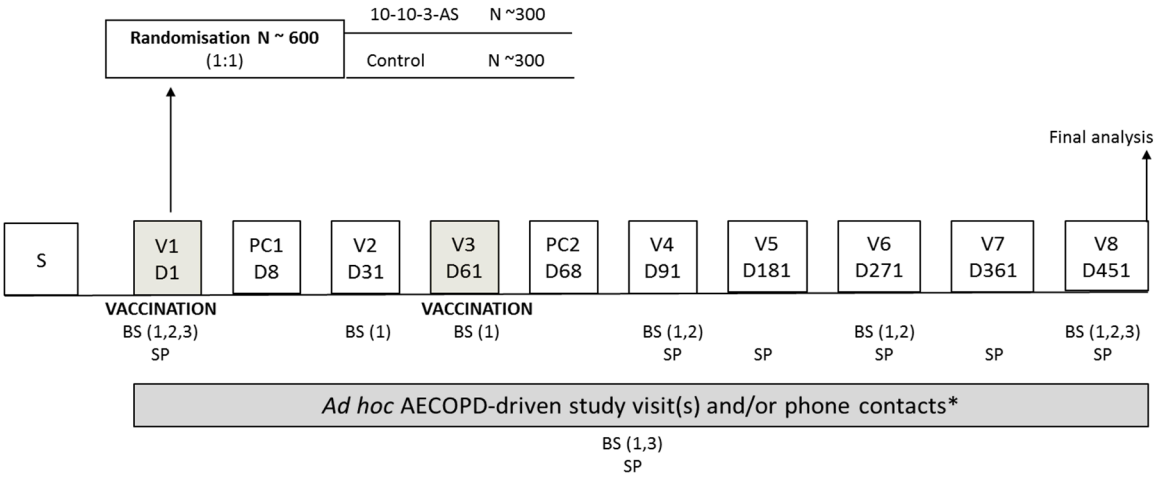
Max	Maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MCAR	Missing Completed at Random
Min	Minimum value
mTVC	modified Total vaccinated cohort
PCR	Polymerase chain reaction
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SERM	Safety Evaluation & Risk Management
SOC	System Organ Class
SRT	Safety review team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated cohort
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
23 OCT 2017	Final version: v1	Final Version 2: 07 JUN 2017
13 FEB 2018	Amendment 1 Final v2: To align with the changes in the Protocol Amendment	Amendment 1 Final: 30 NOV 2017
29 NOV 2019	Amendment 2 Final v3: The following points were implemented: - Fix few typos and explain how solicited Adverse Events collected after day 7 will be analysed. - Update the tertiary objectives, endpoints and analysis section, adding acquisition/apparition analysis according to protocol amendment 2 and describe these analyses in the statistical section. - Add an efficacy analysis by Inhaled Corticosteroids use. - Update the ELISA cut-offs (Table 2) according to protocol Amendment 2. - Add the details of a statistical test to detect a trend in AECOPD rates, by 3 months period. - Add an additional analysis of “responder subjects” according to CAT and SGRQ scores. - Add technical details about qPCR analysis (tertiary objective) - Add details about the prioritization and steps in which the analyses will be performed.	Amendment 2 Final: 27 MAR 2019

2. STUDY DESIGN

Figure 1 Study design overview



S = Screening Visit; V = Visit; PC = Phone contact; D = Day; FU = Follow-up; BS (1) = blood sample for humoral immunogenicity; BS (2) = blood sample for cell-mediated immunogenicity (CMI), this blood sample will only be collected from a sub-cohort of subjects; BS (3) blood sample for biomarkers; SP = sputum sample
The allowed maximum interval between Screening Visit and Visit 1 is 29 days. If a delay occurs for an eligible subject so that the interval exceeds 29 days, some study procedures performed during the Screening Visit needs to be repeated repeated within 7 days (see Table 6 of the protocol for more details).
* An AECOPD visit should be scheduled as soon as possible after the onset of AECOPD symptoms (max 96 hours after and, if applicable, preferably before starting treatment with antibiotics) During this visit blood and sputum samples will be collected. In addition, follow-up phone call(s) and/or visit(s) will take place to determine the end of the AECOPD. These contacts will take place at least every 2 weeks until the AECOPD is resolved.

Investigational vaccine and placebo will be administered in addition to standard of care.

- **Experimental design:** Phase IIB, randomised, observer-blind, placebo-controlled, multi-centric study with two parallel groups.
- **Duration of the study:** for each subject enrolled, the study will last approximately 15 months from Visit 1 up to study completion (Visit 8).
  - Epoch 001: Screening Visit (Day -28 to Day -1).
  - Epoch 002 : Primary starting at Visit 1 (Day 1) and ending at Visit 8 (Day 451).
- **Primary completion Date (PCD):** Last Subject Last Visit (LSLV) from Visit 8 (Day 451) or last visit/contact of Epoch 002.
- **Study groups:**
  - **10-10-3-AS**: Approximately 300 subjects receiving two 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.
  - **CONTROL**: Approximately 300 subjects receiving two doses of placebo (PBS).

The following group names will be used for the statistical analysis

Table 1 Study groups and epochs foreseen in the study

Group order in tables	Number of subjects	Group label in tables	Group definition for footnote
1	~300	10-10-3-AS	2 doses of AS01E-adjuvanted NTHI/Mcat vaccine containing 10 mcg of PD, PE-PilA and 3 mcg of UspA2
2	~300	PLACEBO	2 doses of phosphate buffered solution

- **Sampling schedule:**
  - **Blood samples for assessment of humoral immunogenicity** will be collected from all subjects at Visit 1 (Day 1), Visit 2 (Day 31), Visit 3 (Day 61), Visit 4 (Day 91), Visit 6 (Day 271), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
  - **Blood samples for assessment of cell-mediated immunogenicity (CMI)** will be collected from all subjects in the CMI sub-cohort (approximately 60 subjects in each group) at Visit 1 (Day 1), Visit 4 (Day 91), Visit 6 (Day 271) and at Visit 8 (Day 451).
  - **Blood samples for biomarkers** will be collected from all subjects at Visit 1 (Day 1), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
  - **Blood sample for haematology profile** will only be collected at Visit 1.
  - **Sputum samples for PCR** (all subjects) **and culture** (50% of subjects) will be collected from all subjects at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 271), Visit 7 (Day 361), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.

Other assessments:

- **COPD symptoms:** All subjects will be asked to record COPD symptoms in their electronic Diary Card:
  - Daily in the morning throughout the study (including during AECOPD): **morning symptoms questionnaire**.
  - Daily in the evening throughout the study (including during AECOPD): **EXACT-PRO questionnaire**.
- **HRQOL assessments:**
  - All subjects will be asked to complete the COPD assessment test (CAT) at the Screening Visit (pre-Day 1), Visit 6 (Day 271), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
  - All subjects will be asked to complete St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) at the Screening Visit (pre-Day 1), Visit 6 (Day 271), at Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.

Pre- and post-bronchodilator spirometry assessments will be done for all subjects at the Screening Visit (pre-Day 1), Visit 6 (Day 271) and at Visit 8 (Day 451).

3. OBJECTIVES

3.1. Primary objective

- To assess efficacy of the investigational vaccine as compared to the placebo control with respect to the rate of moderate and severe AECOPDs.

3.2. Secondary objectives

- To describe the safety and reactogenicity of the investigational vaccine.
- To assess efficacy of the investigational vaccine as compared to the placebo control with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe).
- To assess efficacy of the investigational vaccine as compared to placebo with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe) associated with NTHi and/or Mcat detected by PCR.
- To evaluate the humoral immunogenicity of the investigational vaccine.
- To evaluate the cellular immunogenicity of the investigational vaccine.

3.3. Tertiary objectives

- To evaluate the effect of the investigational vaccine on the presence, acquisition/apparition and load of NTHi and/or Mcat at stable visits and AECOPD by PCR.
- To evaluate the effect of the investigational vaccine on the presence, acquisition/apparition and load of NTHi and/or Mcat at stable visits and AECOPD in a subset of sputum samples by culture.
- To explore the efficacy of the investigational vaccine as compared to placebo with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe) associated with NTHi and/or Mcat detected in a subset of sputum samples by culture.
- To explore the impact of the investigational vaccine on health-related quality of life (HRQOL).
- To explore the impact of the investigational vaccine on use of medication for COPD and Healthcare Resource Utilisation.
- To explore the impact of the investigational vaccine on lung function.
- To describe selected biomarkers in stable COPD and during AECOPD.
- To explore the T helper profile of the PD-, PE-, PilA-, UspA2-specific $CD4^+$/ $CD8^+$ T cell responses.

- To collect blood and sputum samples for assay development, for lung microbiome analysis, to explore the level of inflammation (into the lung) and/ or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.
- To explore the data for an immune correlate of protection.

4. ENDPOINTS

4.1. Primary endpoint

- Rate of moderate and severe AECOPD (any cause), occurring within a period starting 1 month post-Dose 2 and lasting for 1 year.

4.2. Secondary endpoints

Safety:

- Occurrence of each solicited local AE, during the 7-day follow-up period (Day 1 - Day 7) following each vaccination.
- Occurrence of each solicited general AE, during the 7-day follow-up period (Day 1 - Day 7) following each vaccination.
- Occurrence of any unsolicited AE, during the 30-day follow-up period (Day 1 - Day 30) following each vaccination.
- Occurrence of any pIMD from first vaccination up to study conclusion.
- Occurrence of any SAE from first vaccination up to study conclusion.

Efficacy: All AECOPD

- Yearly rate of all AECOPD (any cause, any severity) starting 1 month post-Dose 2, in vaccinated and control subjects.
  - Rate of moderate and severe AECOPD cases in vaccinated and control subjects, during 3, 6 and 9 months observation starting 1 month post-Dose 2.
  - Rate of all AECOPD cases in vaccinated and control subjects, during 3, 6, 9 and 12 months observation starting 1 month post-Dose 2.
  - Rate of all AECOPD cases in vaccinated and control subjects, during 3, 6, 9 and 12 months observation starting 1 month post-Dose 2, by severity.
- Time to first moderate or severe AECOPD.
- Time to first AECOPD of any severity.
- Time to first AECOPD, by severity.
- Duration of moderate and severe AECOPDs.
- Duration of AECOPDs of any severity.
- Duration of AECOPDs, by severity.

Efficacy: AECOPD associated to bacteriological pathogens (PCR)

- Rate of NTHi-associated and/ or Mcat-associated moderate and severe AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year.
- Rate of NTHi-associated and/ or Mcat-associated any severity AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year.
- Rate of NTHi-associated and/ or Mcat-associated AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year, by severity.
- Time to first moderate or severe NTHi-associated and/ or Mcat-associated AECOPD.
- Time to first NTHi-associated and/or Mcat-associated AECOPD of any severity.
- Time to first NTHi-associated and/or Mcat-associated AECOPD, by severity.
- Duration of moderate and severe NTHi-associated and Mcat-associated AECOPD.
- Duration of NTHi-associated and/or Mcat-associated AECOPDs of any severity.
- Duration of NTHi-associated and/or Mcat-associated AECOPD, by severity.

Immunogenicity and CMI:

- Anti-PD, anti-PE, anti-PilA and anti-UspA2 total IgG antibody concentrations as measured by ELISA at Day 1, Day 31, Day 61, Day 91, Day 271 and at Day 451, in all subjects.
- 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 271 and at Day 451, in a sub-cohort of subjects.

4.3. Tertiary endpoints

Sputum sample PCR:

- Occurrence (presence and absence), bacterial load measured by PCR of NTHi and/or Mcat in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD visit.
- Number of acquisitions and apparitions of NTHi and Mcat bacteria in sputum collected from Day 1 and from Day 91 and analysed by PCR.

Sputum sample culture:

- Occurrence (presence and absence), and semi-quantitative bacterial load measured in a subset of sputum sample by culture of NTHi and/or Mcat in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD visit.

- Number of acquisitions and with apparitions of NTHi and Mcat bacteria in sputum collected from Day 1 and from Day 91 and analysed by culture.
- Rate of NTHi-associated and Mcat-associated, moderate and severe AECOPD.
- Rate of NTHi-associated and Mcat-associated any severity AECOPD.
- Rate of NTHi-associated and Mcat-associated AECOPD, by severity.
- Time to first moderate or severe NTHi-associated and/or Mcat-associated AECOPD.
- Time to first any NTHi-associated and rate Mcat-associated AECOPD.
- Time to first NTHi-associated and rate Mcat-associated AECOPD, by severity.
- Duration of each moderate and severe NTHi-associated and Mcat-associated AECOPD.
- Duration of NTHi-associated and/or Mcat-associated AECOPDs of any severity.
- Duration of NTHi-associated and/or Mcat-associated AECOPD, by severity.

QOL:

- Assessment of EXACT-PRO score, daily in the evening throughout the study, in all subjects.
- Assessment of CAT scores at Screening, Day 271 and Day 451, and from first vaccination to study conclusion for each AECOPD visit, in all subjects.
- Assessment of SGRQ-C score at Screening, Day 271 and Day 451, and from first vaccination to study conclusion for each AECOPD visit, in all subjects.
- Assessment of use of medication to treat (AE)COPD and healthcare utilization in all subjects throughout the study period.

Lung function:

- Assessment of FEV1% of predicted normal value at Screening, Day 271 and Day 451, in all subjects.

Biomarkers:

- Concentration of selected biomarkers (fibrinogen, hsCRP and IP-10), at Day 1 and Day 451, and for each AECOPD visit from first vaccination to study conclusion.

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 271 and Day 451

Assay development, viral pathogen in sputum, microbiome analysis and lung inflammation:

- Presence of respiratory viral pathogens in sputum (including respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) at Day 1, Day 91, Day 181, Day 271, Day 361, Day 451 and at each AECOPD visit from first vaccination to study conclusion.
- Presence and/or concentration of inflammatory cytokines in sputum at Day 1, Day 91, Day 181, Day 271, Day 361, Day 451 and at each AECOPD visit from first vaccination to study conclusion on a subset of samples.
- Further characterization of *H. influenzae* and *M. catarrhalis* strains may be performed generating microbiome data to investigate on the impact of vaccines in Haemophilus relative abundance, Moraxella richness and relative abundance and relative abundance of other taxa, overall diversity in sputum (Shannon diversity index) and number of OTUs (descriptive). Details of the statistical analyses will be released in a separate additional analysis request.

5. ANALYSIS SETS

5.1. Definition

All enrolled set: All subjects who will sign the inform consent and for whom a subject code is assigned

The following study cohorts will be evaluated.

5.1.1. All enrolled set

All subjects who will sign the inform consent and for whom a subject number is assigned.

Note: ‘Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are tracked in the clinical database but are not considered enrolled.

5.1.2. Total vaccinated cohort

The total vaccinated cohort (TVC-also called Exposed Set-ES) will include all subjects with at least 1 documented study vaccine administration:

- A **safety** analysis based on the TVC/ES will include all subjects with at least one vaccine dose administered and who provided safety data.
- An **immunogenicity/CMI/efficacy** analysis based on the TVC will include all vaccinated subjects for whom immunogenicity/CMI/efficacy data are available.

Moreover, a solicited **TVC set (or solicited safety set)** will include all subjects with at least one vaccine dose administered and who provided solicited safety data during the 7 days reporting period. All the analyses related to solicited AEs will be conducted using this analysis set.

Note: for subjects receiving only one dose the efficacy endpoint is the number of moderate or severe AECOPD (any cause), occurring during 12 months observation period.

The TVC analysis will be performed per treatment actually administered at Dose 1.

5.1.3. Modified total vaccinated cohort

The modified total vaccinated cohort (mTVC) will include all subjects with 2 documented study vaccine administrations with respect to the vaccine actually administered.

The primary efficacy analysis will be performed on the mTVC.

5.1.4. Full Analysis set (FAS)

The FAS will include all randomized subjects who will receive at least 1 vaccine administration. As per intention-to-treat (ITT) principle, a subject in the FAS will be analysed “as randomized” (i.e. according to the vaccine a subject was planned to receive irrespectively of his/her real exposure).

5.1.5. Per- protocol set for analysis of efficacy

The Per-Protocol Set (PPS) for analysis of efficacy will include all subjects in the TVC:

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule.
- Who received the study vaccine according to protocol procedures.
- Who did not received a medication/ product/ vaccine that may have an impact on the efficacy or bacteriological load.

  In addition, for the Bacteriological efficacy endpoints:

- For whom the sputum sample results are available.

5.1.6. Per-protocol set for analysis of immunogenicity and CMI

The PPS cohort for immunogenicity/CMI will include all subjects in the TVC:

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule.
- 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 for immunogenicity/CMI
- Who did not present an intercurrent medical condition leading to elimination from the PPS analysis for immunogenicity/CMI.
- Who complied with the blood sample timings.
- For whom post-vaccination immunogenicity/CMI results are available.

In addition, a PPS set for biomarker analysis will include all subjects who comply with the first 4 points above and for whom biomarker data are available.

Note: each of the above reasons for exclusion will be evaluated for each strain and each time point and thus different strains and time points could present different numbers of observations (N).

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 (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 (previous called TVC)

Code 1030.2 (2nd dose of vaccine not administered at all) will be used to identify subjects eliminated by mTVC.

Code 1160 will be used to identify subjects who did not complete e-Diary for the period Day 1-Day 7 after vaccination and will be eliminated form Safety TVC/ES for the solicited analysis

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

5.2.2.1. Excluded subjects

A subject will be excluded from the PPS 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
1030.2	2nd dose of 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)
2040	Administration of any medication forbidden by the protocol
2050	Developed a withdrawal criterion but was not withdrawn
2080	Subjects did not comply with vaccination schedule
2090.a	Subjects did not comply with blood sample schedule (for Elisa)
2090.b	Subjects did not comply with sputum sample schedule
2090.c	Subjects did not comply with blood sample schedule (for CMI)
2090.d	Subjects did not comply with blood sample schedule (for biomarker)
2100.a	Serological results not available post-vaccination
2100.b	Sputum results not available post-vaccination
2100.c	CMI results not available post-vaccination for those in CMI subset
2100.d	Blood Biomarker results not available post-vaccination
2120.a	Obvious incoherence or abnormality or error in immune data
2120.b	Obvious incoherence or abnormality or error in Efficacy (sputum) data
2120.c	Obvious incoherence or abnormality or error in CMI data
2120.d	Obvious incoherence or abnormality or error in biomarkers data
2130.a	Subject bled for immuno but not planned to be bled
2130.c	Subject bled for CMI but not planned to be bled
2130.d	Subject bled for biomarker but not planned to be bled

5.2.2.2. 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
1060.x+	Unblinding of subjects
1070.x+	Subjects got vaccinated with the correct vaccine but containing a lower volume
1040.x	Subjects receive a vaccination forbidden by the protocol
2040.x+	Subjects receive a medication forbidden by the protocol

5.2.2.3. Visit-specific censored Data

Data from visit x will be censored 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
2090.x.y	Subjects did not comply with blood/sputum sample schedule at visit x
2100.a.x	Serological results not available for blood sample at visit x
2100.b.x	Bacteriological results not available for sputum sample at visit x
2130.x.y	Subject bled but not planned to be bled

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

The following important protocol deviations, which will not lead to elimination from analysis, will be reported by groups:

- Manual randomization: In case of the randomization system is unavailable, the investigator has the option to call help desk and to perform a ‘manual’ randomization, which will be documented accordingly.
- In case unexpected vaccinations at study start were granted due to regulatory recommendation, the subjects who had such vaccination could be mentioned.
- Subjects for whom the spirometry could not be performed.
- Subjects without chest X-ray available
- Subjects of childbearing potential without pregnancy test for whom the pregnancy did not happen.
- Possible violation from lab manual having no impact on sputum or blood results
- Subject outside of AECOPD Visit windows

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Section 11 and will not be repeated below.

6.1. Demography

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

Demographic and baseline characteristics: age (in years), gender, ethnicity, smoking status at enrolment (i.e., screening visit) will be summarised by group using descriptive statistics.

Other variables GOLD grade at baseline, history of moderate and severe exacerbation in the last 12 months (<2 or ≥ 2, and total number), HRQOL baseline scores from CAT, SGRQ-C at enrolment visit (i.e., screening visit) will also be summarized as baseline characteristics.

- Frequency tables will be generated for categorical variable such as gender; geographical ancestry, age category, GOLD, smoking status and history of moderate and severe exacerbation;
- N, mean, median, standard deviation (SD) and min and max values will be provided for continuous data such as age, height, weight, body mass index (BMI), total number of exacerbation in previous 12 months and HRQOL baseline scores.

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

- Age in year (as continuous variable),
- Age category: 40-59 y, 60-80y
- Gender: Male, Female
- Race: (all reported in e-CRF)
- Ethnicity: Hispanic or Latino, Not Hispanic nor Latino
- Exacerbations in previous 12 months:
  - Total number
  - Mild
  - Moderate
  - Severe
- Exacerbations in previous 12 months category: <2, >=2
- Smoking status: yes, no
- Pack year (as continuous variable)

- GOLD grade category: 1 mild, 2 moderate, 3 severe, 4 very severe
- FE1/FVC category: >=70, <70
- CMI sub-cohort: yes, no
- Culture cohort: yes, no

The following variables will be included in vital sign summary and listing:

- Height (cm)
- Weight (kg)
- Body temperature (continuous variable)
- Body temperature category < 37.5°C, ≥ 37.5°C
- Hear rate
- Respiratory rate
- Systolic Blood Pressure,
- Diastolic Blood Pressure,
- Chest x-ray result: yes, no
  - Infiltrate presence (%): unilateral, bilateral
  - Pleural effusion (%): right chest, left chest, bilateral

Demographic and baseline characteristics will be tabulated for the Exposed Set (TVC) and mTVC, and no inferential analyses of are planned.

The distribution of subjects enrolled among the study sites and country will be tabulated as a whole and per group.

Number and percentages of subjects in each study cohorts (All enrolled, TVC, mTVC, FAS and PPS) will be summarized by 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 any cohort of analyses will be tabulated.

6.1.2. Additional considerations

Physical examination:

- As part of the baseline characteristics, variables collected during the physical examination such as height, weight, BMI, pulmonary function test baseline values (such as FEV_1/FVC, FEV_1 and FEV_1 % of predicted), body temperature, heart rate, respiratory rate, Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values will be summarized by the mean of descriptive statistics.

Body temperature will be also categorized as Fever YES (≥ 37.5°C (99.5°F)) or NO (< 37.5°C (99.5°F))

Haematology profile:

Haematology profile is defined at visit 1 only and the following parameters will be analysed form whole blood:

Whole blood	Leukocytes (White Blood Cells) Neutrophils Lymphocytes Eosinophils Basophils Monocytes Erythrocytes (Red Blood Cells) Hemoglobin Platelets

For each group and for each **haematology parameter** descriptive statistics such as: mean, median, standard deviation, minimum and maximum will be tabulated, together with the percentage of subjects having results below or above laboratory normal ranges.

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.
- Similarly, the frequencies and percentage of subject who received influenza or pneumococcal vaccination in the previous 12 months before enrollment will be reported overall and by vaccine group

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccinations will be summarized overall and by vaccine group. Data will be tabulated for the Exposed Set.

6.2.2. Additional considerations

None.

6.3. Efficacy/Effectiveness

Efficacy of the vaccine will be evaluated as both primary and secondary endpoints.

In the primary endpoint analysis, the 'clinical' vaccine efficacy is defined as reduction in 12 months rate of moderate and severe AECOPD (any cause) from one month after complete vaccine exposure.

In secondary endpoints a broader definition for efficacy is being investigated and the following rates are considered:

- Reduction in 3, 6, and 9 months rate of moderate and severe of AECOPD (any cause) starting from one month after complete vaccine exposure.
- Reduction in yearly rate of any grading of AECOPD (any cause) starting from one month after complete vaccine.
- Reduction in severity of AECOPD (any cause) starting from one month after complete vaccine.
- Reduction in yearly rate of moderate and severe of AECOPD associated with NTHi or Mcat, starting from one month after complete vaccine.
- Reduction in yearly rate of any grading of AECOPD associated with NTHi or Mcat, starting from one month after complete vaccine.
- Reduction in 3, 6, and 9 months rate of moderate and severe AECOPD associated with NTHi or Mcat starting from one month after complete vaccine exposure.
- Reduction in severity of AECOPD associated with NTHi or Mcat starting from one month after complete vaccine.

6.3.1. Analysis of efficacy planned in the protocol

The efficacy analysis will be performed on the mTVC and repeated on the TVC and on the FAS. The primary efficacy analysis will also be repeated on the PPS if the percentage of vaccinated subjects excluded from the PPS for efficacy is more than 5%.

In the TVC cohort, if a subject receives only one dose the efficacy endpoint is defined as the number of (moderate or severe) AECOPD (any cause), occurring within a period starting from Day 90 and lasting for 1 year (i.e., until study conclusion).

Vaccine efficacy (VE) is expected to start at 1 month post-Dose 2 (Day 90), so the study period is divided in to two: from enrolment (Day 1 - day of first injection) up to one month post Dose 2 (Day 90) and from one month post Dose 2 (Day 90) until study end (Day 451).

Evaluation of VE and incidence rate of AECOPD in both study groups, together with CIs will be computed for each study periods.

6.3.1.1. Efficacy – Clinical Endpoints

6.3.1.1.1. Primary Analyses

The primary analysis method of the vaccine VE will consider the exact inference on the risk ratio (R_{vacc} / R_{con}) based the total number of moderate and severe AECOPD observed in 1 year time of follow up.

VE is defined as: $VE = 1 - R_{vacc} / R_{con}$

being

- R_{vacc} = average yearly incidence rate of AECOPD events per subject in the group 10-10-3-AS.
- R_{con} = average yearly incidence rate of AECOPD events per subject in the placebo group.

Inferential statistic

Incidence rates and VE with 87% and 95% CIs will be tabulated for primary efficacy endpoint. P-value (to test H_0 = [VE=0]) will be tabulated for the primary endpoint.

The efficacy of vaccine in preventing moderate and severe AECOPD will be demonstrated if the lower limit of the two-sided 87% CI of VE is above 0.

The primary outcome will be analysed using the Negative Binomial regression model with number of AECOPD as dependent variable; treatment (vaccine or placebo), age group (40 - 59 yrs or 60 - 80 yrs), GOLD grade (2, 3 or 4) and history of moderate and severe exacerbations (<2 or ≥ 2) and country as independent variables, with logarithm as link function, and the logarithm of time for follow-up (in days) as an offset variable.

The following SAS code will be applied for primary analysis:

```
PROC GENMOD data=<dataset>;
 CLASS trt age gold hexac country;
 MODEL nb_exac = trt age gold hexac country
      / dist=NegBin LINK=log OFFSET=logfu alpha=0.13;
RUN;
```

Where
trt= treatment arm;
age= Age Group;
nb_exac=number of exacerbations;
gold= GOLD grade at enrolment;
hexac= History of moderate/severe exacerbation;
country=Subject Country;
fu= follow up time in days;
logfu= log(fu);

Point estimate and CIs of the incidence rate for each arm, will be computed using a simple Negative Binomial model, without covariates and thus the following SAS code will be applied:

```
PROC GENMOD data=<dataset>;
BY trt;
MODEL nb_exac =       / dist =NegBin LINK=LOG OFFSET=LOGFU alpha=0.05;
ODS OUTPUT ParameterEstimates=out_parm NObs=Nobs;
RUN;

DATA parm_est(keep= val rate rate_LL rate_UL);
 SET out_parm(WHERE=(Parameter='Intercept'));
 format rate rate_LL rate_UL 8.2;
      val= "Yearly Rate from Negative Binomial";
      rate=EXP(Estimate)*365;
      rate_LL=EXP(LowerWaldCL)*365;
      rate_UL=EXP(UpperWaldCL)*365;
 RUN;
```

Note: If the model does not converge, the Poisson distribution will be used instead of the Negative Binomial.

The number of AECOPD occurring from enrolment up to 1 month post-Dose 2 will be used as 'baseline' value. No difference between vaccine and placebo is expected in this period.

Descriptive statistics

For each treatment group, the total number of subjects, total number of AECOPD, total exposure time (in days), and incidence exacerbation rate (per year and per each sub period considered) together with the frequency of number of AECOPD will be tabulated.

The following statistics will be reported for exacerbation rate in the two treatment groups: N, mean, SD, median, Q1, Q3, min and max.

Sensitivity analysis

Primary analysis will be presented in three study populations: mTVC, TVC, FAS and PPS. In addition, a sensitivity analysis will be carried out using permutation test.

Permutation test procedure

The null distribution of Z to test H0 (i.e., β=0 or VE=0) will be obtained by re-randomizing treatment assignment according to the original minimization algorithm (Section 11.3) while keeping outcomes and covariates as observed. The procedure to follow is described below:

1. Fit the regression model to obtain the test statistic Z to test H_0 (i.e., β=0 or VE=0)
2. Estimate the null distribution for the test statistic Z with N (=10000) replicates of the two following steps:

a. Re-randomize treatment assignment using minimization.

b. Re-fit the regression model to re-derive the test Z

3. Derive the empirical p-value for the test statistic Z from the null distribution based on the permutation distribution

$p_{(\text{permutation test})}=(M)/(N)$

Where M denotes the number of replicates for which the test statistic Z obtained in the permutation procedure is equal to or greater than (in absolute value) the observed value of Z obtained in 1, and N denotes the number of replicates (i.e., 10000).

6.3.1.1.2. Secondary Analyses

Incidence rate of AECOPD

The following incidence rates of AECOPD (any type) occurring from enrolment up to 1 month post-Dose 2 will be computed together with 95% CIs, and incidence rates together with VE in the prevention of AECOPD (any type) will be computed over a period starting 1 month post-Dose 2 and lasting for 1 year, with 95% CIs:

- Any severity of AECOPD.
- AECOPD, by event severity.

Time to first AECOPD event

The time to first AECOPD events following complete schedule vaccination (i.e., 1 months post-Dose 2) will be analysed using Cox's proportional hazard regression model which include, with treatment, GOLD grade at enrolment (2, 3 or 4) and history of exacerbations (<2 or ≥ 2) as factors. Wald test and CIs will be produced.

The time to first event will be computed for the following:

- Time to first moderate and severe AECOPD
- Time to first any severity AECOPD.
- Time to first AECOPD, by event severity.

Hazard rate and CI will be derived using the following SAS code:

```
PROC PHREG data=<dataset>;
CLASS trt age gold hexac;
MODEL survtime*status(0)=trt age gold hexac / TIES=EXACT RISKLIMITS;
RUN;
```

In addition the survival curves for each vaccine group will be calculated non-parametrically, and presented graphically using the Kaplan-Meier (i.e., Product-Limit) method, using the following code:

```
PROC LIFETEST data=<dataset> method =KM plot=(survival(atrisk)
logsurv);
TIME survtime*Status(0);
STRATA trt;
RUN;
```

survtime represents variable containing AECOPD times.

status represents censoring variable (0=censored, 1=event).

Duration of AECOPD event

The length (in days) of each AECOPDs will be tabulated and presented via descriptive statistics (mean, SD, median, Q1, Q3, minimum and maximum), for each treatment and for the two periods (before 1 month post-Dose 2 and after 1 month post- Dose 2).

Tables will be produces considering the following:

- Duration of moderate and severe AECOPDs.
- Duration of AECOPDs of any severity.
- Duration of AECOPDs, by severity.

Stratification and additional analysis

Yearly rate of AECOPD and VE, together with 95% CIs, will be computed for the following time periods:

- By 6 Months follow-up period (from 1 month post-Dose 2)
- By 3 Months follow-up period (from 1 month post-Dose 2)

Similarly, for the time-to-event and duration of AECOPD data will be also presented for the entire study period starting from Day 1 up to study termination.

In addition, descriptive statistics for the yearly rates and VE will be presented by patient severity (GOLD grade: 2, 3, or 4), by Country (USA, Canada, France, Spain, Belgium, UK, Germany and Italy), by history of exacerbations (< 2 or ≥ 2), by usage of inhaled corticosteroid at visit 1 (independently on the start date of usage), by eosinophil level at baseline (<2% or ≥ 2%), by NHTi and Mcat presence in sputum at baseline (NTHi alone, Mcat alone, NTHi or Mcat) and by age group (40 - 59 yrs or 60 - 80 yrs).

In addition to the rates of moderate and severe and any severity AECOPD at 3, 6, 9 and 12 months starting 1 month post dose 2, the Kendall-Tau (Kendal Rank correlation Coefficient) test for trend of rates over time will be calculated. A statistically significant correlation between Incidence rates and time period will be concluded if p-value is less than 0.05.

A SAS code similar to the following will be used for this purpose:

```
PROC CORR data=<dataset> kendall;
class treatment;
 var rate month;
by treatmens;
RUN;
```

6.3.1.2. Efficacy – Bacteriological Endpoint (PCR)

An AECOPD will be considered 'associated' to NTHi and/or Mcat if the sputum sample, collected during AECOPD visit, will reveal the presence of those bacteria.

We can assume that more than 99% of *H. influenzae* isolates in sputum (derived from lung) are non-typeable (NTHi) [Wilkinson, 2017] and thus the presence of Hi bacteria in sputum during exacerbation will be used to determine AECOPD associated to NTHi.

In case of no sputum sample at such visit, or no bacteriological presence (i.e., Hi or Mcat) the event will not be counted.

Bacteriological vaccine efficacy (VE_{bact}) is defined as reduction in number of NTHi and/or Mcat associated AECOPD in vaccinated subjects compared to placebo subjects:

$VE_{bact} = 1 - R_{vacc} / R_{con}$

where

- R_{vacc} = average yearly incidence rate of AECOPD events associated to NTHi and/or Mcat per subject in the group 10-10-3-AS.
- R_{con} = average yearly incidence rate of AECOPD events associated to NTHi and/or Mca per subject in the placebo group.

VE_{bact} in prevention of NTHi and/or Mcat associated AECOPD will be evaluated via PCR method in all subjects. The statistical analysis will be performed in a modified TVC (mTVC) population as first line and repeated in the PPS cohort if more than 5% of subjects are excluded.

The mTVC is defined as all subjects in the TVC (i.e. ES) who provide sputum sample results.

The following incidence rate together and VE_{bact} over a period starting 1 month post-Dose 2 and lasting for 1 year and its 95% CIs will be computed:

- NTHi and/or Mcat-associated moderate and severe AECOPD.
- NTHi and/or Mcat-associated all-severity AECOPD.
- NTHi and/or Mcat-associated AECOPD, by severity.
- The time until first moderate and severe NTHi and/or Mcat- associated AECOPD.
- The time until first NTHi and/or Mcat- associated AECOPD (any severity).
- The time until first NTHi and/or Mcat- associated AECOPD by severity.

In addition yearly rates of AECOPD associated to NTHi and/or Mcat, and VE_{bact} , together with 95% CIs will be evaluated for the following time periods:

- By 6 Months follow-up period (from 1 month post-Dose 2)
- By 3 Months follow-up period (from 1 month post-Dose 2)

Inferential statistic

Number and proportion of sputum samples (obtained at each scheduled visit and at each AECOPD visit) positive for bacterial pathogens (Hi and/or Mcat) will be computed together with exact 95% CIs by group and overall. The exact CIs will be estimated assuming independence of bacterial results across sputum samples.

The bacteriological vaccine efficacy outcome will be evaluated using same model as for clinical efficacy with the following SAS code:

```
PROC GENMOD data=<dataset>;
 CLASS trt age gold hexac country;
 MODEL nb__bact_exac = trt age gold hexac country
      / dist=NegBin LINK=log OFFSET=logfu;
RUN;
```

Where

nb_bact_exac are AECOPD associated to NTHi and/or Mcat by PCR method

As for the primary endpoint the number of bacterial associated AECOPD occurring from enrolment up to 1 month post-Dose 2 will be used as 'baseline' value. No difference between vaccine and placebo is expected in this period.

Descriptive statistics

For each treatment group, the total number of subjects, total number of AECOPD associated to NTHi and/or Mcat, total exposure time (in days), incidence of bacteriological associated exacerbation rate (per year and per each sub period considered) and the frequency of number of AECOPD will be tabulated.

The following statistics will be reported for AECOPD associated to NTHi and /or Mcat: N, mean, SD, median, Q1, Q3, min and max.

6.3.1.3. Efficacy – Bacteriological Endpoint (culture)

Same set of analyses, as in the PCR efficacy bacteriological endpoint, will be performed in the subset of subjects for whom the culture sputum (collected at AECOPD visits) is performed

Approximately 50% of the subjects will be allocated to sputum culture analysis (depending on which site the subject belongs as not all sites are qualified and selected for culture analysis).

The selection of sites that will perform the sputum culture is based on site characteristics (i.e., presence of qualified laboratory) and only subjects enrolled in these sites will be considered for this analysis.

The analysis will be performed in the culture-subset of the modified TVC (mTVC) population. The mTVC is defined as all subjects in TVC (ES) and in the subset for culture sample who provide valid culture sputum sample results.

6.3.2. Additional considerations

6.3.2.1. Clinical endpoint

Number of AECOPD

The number of AECOPD occurring during the 1 year follow-up period starting 1 month post-Dose 2 will be used to describe vaccine efficacy (VE). Exacerbation rate reported during this period will be calculated for each subject.

Only for the purpose of reporting summary statistics, the number of exacerbations during the 1-year follow-up will be imputed for subjects withdrawing from the study to provide an estimate of the number of exacerbations over the follow-up period. This calculation will only be performed for the descriptive statistics for the rate of exacerbations during 1 year follow up period since the modelling of exacerbations takes into account the number of exacerbations and the time of follow-up for each subject [see Section 11].

Control of type I error

Inferential analyses for efficacy are planned to be performed at alpha level of 0.13 (two sided). No alpha adjustment for multiple testing in the secondary endpoints will be performed, nevertheless efficacy analysis, both primary and secondary endpoints will be also complemented with the 95% CI.

6.4. Immunogenicity and Cell-mediated Immunity (CMI)

6.4.1. Analysis of immunogenicity planned in the protocol

As first line, the immunogenicity analysis will be based on the PPS (ATP). If the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is more than 10%, a second line immunogenicity analysis will be performed on the TVC.

Within group assessment

For each group (i.e., vaccine and placebo), at each timepoint during which blood samples are collected for humoral immune response (i.e., Day 1, Day 31, Day 61, Day 91, Day 271 and at Day 451), and for each vaccine strain (i.e., PD, PE, PilA and UspA2), the following will be computed:

- Seropositivity* rate and the associated exact 95% CI
- GMCs and the associated 95% CI

* Seropositivity rate is defined a percentage (proportion) of seropositive subjects. Seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value, as specified in Table 2.

Descriptive statistics

The $\log_{10}$ ELISA concentration and fold increase over pre-exposure (i.e., Day 1) will be tabulated via descriptive statistics such as N, mean, SD, median, min, max and 95% CI for each group, study visit (where immune blood draw is performed) and vaccine strain.

Similarly, the proportion of seropositivity subjects will be tabulated together with N, number of seropositive subjects and percentage for each group, study visit and vaccine strain.

In addition, the distribution of antibody concentrations for each strain will be displayed using Reverse Cumulative Distribution Curves (RCDF).

The percentages of subjects with positive (see Table 2) ELISA values (on log10 scale) will be plotted via RCDF, having the individual concentration on the X-axis and the percentage of subject with equal to or greater than the value on the Y-axis by strain and visit.

Between groups assessment

The between groups immunogenicity analysis will be carried out with an alpha =0.05, however these are descriptive comparisons with the aim to characterize the difference between groups and should be interpreted with caution considering that there will be no alpha adjustment for multiplicity.

GMCs and GMCs ratio

The difference between vaccine and placebo will be evaluated in terms of GMCs ratio (Vaccine/Placebo) and it will be tabulated for each time together with the 95% CIs of the GMC ratio between groups by using an ANCOVA model on the logarithm base10 transformation of the concentrations. This model will include the group (vaccine or control), age category (40 - 59 years or 60 - 80 years), GOLD grade (GOLD 2, GOLD 3 or GOLD 4) and country as fixed effects and pre-Dose 1 concentration (as covariate).

For each vaccine group and time point (Visit), adjusted GMCs, GMC ratios and their 95% CIs will be obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% CIs of the log10-transformed concentrations. These will be obtained from an ANCOVA with vaccine group, age category, GOLD grade, country and pre-Dose 1 concentrations, as implemented in the following SAS code:

```
PROC GLM data=<dataset>;
BY visit;
class trt age gold country;
MODEL log(titer) = trt age gold country log(prettier);
LSMEAN trt / CL PDIFF ALPHA=0.05;
RUN;
```

Seropositivity: proportion and difference between proportions.

The vaccine group difference will be also evaluated in terms seropositivity proportion difference calculated using a binomial distribution. For constructing the 2-sided 95% CIs for the difference between groups the usual normal approximation is not considered to be appropriate because these proportions could be close to 1. Therefore, the associated confidence interval for the differences in percentage will be constructed using the MN method [Miettinen and Nurminen, 1985]. In analyzing differences in proportions, the MN method assumes normality of the test statistic (or a chi-square distribution for the squared version) under the null hypothesis and the difference with the usual method is in the variance estimation. This method is implemented in SAS with the following code:

```
PROC FREQ data= <dataset>;
TABLES trt*count / RISKDIFF(CL=MN) ALPHA=0.05;
WEIGHT frequency / zero;
RUN;
```

Table 2 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit*	Cut-off*	Laboratory
SERUM	anti-PD antibody	ELISA	In house	EU/ml	153	GSK Biologicals ** or GSK designated laboratory
	anti-PE antibody				16	
	anti-PilA antibody				8	
	anti-UspA2 IgG antibody				28	

EU/ml = ELISA unit per millilitre
* 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.

6.4.2. Analysis of CMI planned in the protocol

CMI analysis will be descriptive only and it will be performed in a subset of approximately 120 subjects for whom the CMI blood samples are collected (*see protocol* section 5.1 Number of subjects).

CMI analysis will be based on the PPS (ATP). If more than 10% will be excluded from the PPS for CMI, a second line CMI analysis will be performed on the CMI subset of the TVC (i.e., All subjects with at least 1 documented study vaccine administration and for whom CMI data are available).

NTHi and Mcat - specific CMI responses as measured by flow cytometry ICS

Descriptive statistics

For each vaccine strain (PD, PE, PilA and UspA2) the frequency of specific $CD4^+$T-cells producing two or more markers (see Table 3) will be summarised by means of descriptive statistics (mean, SD, minimum, Q1, median, Q3, and maximum) for each group, and at each time point during which blood samples are collected for CMI subset (Day 1, Day 91, Day 271 and Day 451).

The frequency of CD4+ T-cells producing two or more markers upon in vitro stimulation with the antigen (induction condition) is presented per million of CD4+ T cells for the analysis and in percentage for the graphical representation (via BOX-plot).

The Geometric Mean (GM) frequency at each CMI timepoint (Day 1, Day 91, Day 271 and Day 451) and for each stimulation (vaccine antigen) will be also computed by taking the anti-log of the mean of the log frequency transformations.

Table 3 Intracellular cytokines staining (Markers)

Method	Unit	Cytokine	Cytokine Label
Flow cytometry ICS	Number of specific CD4+T-cells /10^6	CD40L	CD40 Ligand
		IL-2	interleukin 2
		IL-13	interleukin 13
		IL-17	interleukin 17
		IFN-γ	interferon gamma
		TNF-α	tumour necrosis factor alpha

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 time point: Day 1, Day 91, Day 271 and Day 451 and via BOX plot.

6.4.3. Additional considerations

Humoral immune response

Missing immunogenicity data are considered missing completed at random (MCAR) and therefore will not contain information that impact the results of the analysis (i.e., not informative). Imputation methods will therefore not be used.

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.

Cell-mediated immune response

The frequency of CD4+ T-cells expressing a marker (see Table 3) is presented per million of cells for the analysis and per hundred cells for the graphical representation.

The frequency of antigen-specific CD4+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ T-cells producing at least 2 cytokines, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ T-cells producing at least 2 cytokines upon in vitro stimulation in medium only (background condition).

$$\boldsymbol{Freq}^{2+}_{\boldsymbol{Induction}} = \frac{\boldsymbol{n}^{2+}_{\boldsymbol{Induction}} - \boldsymbol{n}^{2+}_{\boldsymbol{background}}}{\mathbf{1000000}} \quad \boldsymbol{Log_e}\left(\boldsymbol{Freq}^{2+}_{\boldsymbol{Induction}}\right) = \boldsymbol{Log_e}\left(\frac{\boldsymbol{n}^{2+}_{\boldsymbol{Induction}} - \boldsymbol{n}^{2+}_{\boldsymbol{background}}}{\mathbf{1000000}}\right)$$

$n^{2+}_{Induction}$ = Number of antigen-specific CD4+T-cells expressing two or more cytokines.

Each data will be obtained by subtracting the summary of the background value to each summary value. Values less than or equal to zero will be set to 1 for the purpose of geometric mean calculation and graphical representation.

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The safety analysis will be based on the ES (also called TVC).

All analyses will be based on the 'as treated' analysis set.

Safety analysis will be descriptive, no inference and formal statistical comparison is planned for the safety data.

Safety reporting period differs depending on safety endpoints. Table 4 shows the overview of the safety reporting

Table 4 Reporting periods for collecting safety information

Event	Screening Visit*	Visit 1 Dose 1	6 d post Dose 1	29 d post Dose 1	Visit 3 Dose 2	6 d post Dose 2	29 d post Dose 2	6 m post Dose 2	Study Concl
Timepoint		Day 1	Day 7	Day 30	Day 61	Day 67	Day 90	Day 241	Day 451
Solicited local and general AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
SAEs									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									
pIMDs									
Intercurrent medical conditions									

* i.e. consent obtained.
The double-bordered lines indicate timings of vaccination.
AE = adverse event; SAE = Severe adverse event; GSK = GlaxoSmithKline; pIMD = potential immune mediated diseases

6.5.1.1. Solicited Local and General Adverse Events:

The following local AE will be solicited for 7 days after each vaccination:

Table 5 Solicited local adverse events:

Local AE	Grading	Collection period
at injection site	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
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 Day 61-Day 67
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 diameter0	Day 1-Day 7 Day 61-Day 67

The percentage of subjects with at least one local solicited AE reported in diary card within 7 days after each dose (Day 1-Day 7) will be tabulated together with the exact 95% CI. Similarly, the percentage of doses followed by at least one local solicited AE will be tabulated together with the exact 95% CIs within each group. The percentage of subject with grade 3 solicited AEs lasting for at least two days will be reported, for each group, by vaccination and overall.

The same tabulation will be done for grade 3 solicited local AEs.

The following general AE will be solicited for 7 days after each vaccination:

Table 6 Solicited general adverse events:

General AE	Grading	Collection period
Headache	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Fatigue	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Myalgia	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Chills	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
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 Day 61-Day 67

The percentage of subjects with at least one general solicited AE reported in diary card within 7 days after each dose (Day 1-Day 7) will be tabulated together with the exact 95% CI. Similarly, the percentage of doses followed by at least one general solicited AE will be tabulated together with the exact 95% CIs within each group.

The exact 95% CIs will be calculated assuming independence between doses

The same tabulation will be done for grade 3 solicited general AEs.

The percentage of subjects reporting each individual local and general solicited AEs during the solicited follow-up period (i.e., day of vaccination and six subsequent days after each vaccination) by grading will be tabulated with exact 95% CI after each dose and overall by group. The percentage of doses followed by each individual solicited local and general AE will be tabulated overall by group with exact 95% CIs [Clopper CJ, Pearson ES. 1934]

The exact 95% CIs will be calculated assuming independence between doses.

For fever (irrespective of route of measurement), additional analyses will be performed 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

6.5.1.2. Unsolicited Adverse Events:

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 e-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 (SOC) and preferred term within SOC. 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.

The percentage of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) during a 30-day follow-up period after each dose (Day 1 –Day 30) will be tabulated with exact 95% CI for each group. The same tabulation will be performed by severity, and for unsolicited AEs with a relationship to vaccination.

SAEs, death, pIMDs and AE leading to withdrawal reported during the entire study will be tabulated (from Day 1 until study termination) and listed.

In addition, SAEs related to study participation or concurrent GSK medication/vaccine reported from inform consent signed until entire study duration will be also listed.

This study foreseen two injections (i.e., two vaccinations) for each subject, and thus unsolicited AEs summary tables will be presented overall and by period of onset and will include frequency distributions of the different adverse events:

Number and percentage of subjects with the following AEs will be computed:

Onset between day 1 and Day 30 after each vaccination:

- Any AE after each vaccination (overall)
- Any AE after each vaccination, by vaccination
- By severity AE after each vaccination (overall)
- By AE severity after each vaccination, by vaccination
- Related unsolicited AEs after each vaccination (overall)
- Related unsolicited AEs after each vaccination by vaccination
- Related unsolicited AEs by severe after each vaccination (overall)
- Related unsolicited AEs by severe after each vaccination by vaccination
- Any medically attended unsolicited AE (overall).
- Any medically attended unsolicited AE, by vaccination

Onset between day 1 and Day 450 (study termination):

- Any serious adverse events (SAE) (overall).
- Any serious adverse events (SAE) by vaccination.
- Related SAE (overall).
- Any AE leading to death (overall).
- Any unsolicited AE leading to premature withdrawal from study (overall).
- Any potential immune mediated diseases (overall)
- Any potential immune mediated diseases by vaccination
- Any AE leading to hospitalization (overall).

Onset between Screening and Day 450 (study termination):

- Any SAE related to study participation (overall).

6.5.2. Additional considerations

For solicited symptoms, missing or unevaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the TVC (also called ES) will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

Solicited adverse events continuing beyond day 7 will be followed until resolution (up to Day 30).

For the unsolicited symptoms and concomitant medications/ products/ vaccinations, all vaccinated subjects will be considered and subjects who miss reporting symptoms/concomitant medications/ products/ vaccinations will be treated as subjects without unsolicited symptoms or concomitant medications/ products/ vaccinations, respectively.

6.5.2.1. Exclusion of implausible solicited Adverse Event

Some local and general 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 below:

Table 7 Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Redness	≥ 900 mm < 0 mm
Swelling	≥ 500 mm < 0 mm

6.5.2.2. 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:

Table 8 MedDRA coding for solicited AE

Solicited symptom	PT term code	Corresponding PT 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	10037660	Pyrexia

The following results will be tabulated:

The percentage of subjects with at least one **local type AE** (solicited and unsolicited), with at least **one general** adverse event (solicited and unsolicited) and with **any AE** during the solicited follow-up period, i.e., the day of vaccination and six subsequent days after each vaccination will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be done for grade 3 AEs.

The percentage of doses followed by at least one **local AE** (solicited and unsolicited), by at least one **general AE** (solicited and unsolicited) and by **any type AE** will be tabulated, overall vaccination course, with exact 95% CI. The same tabulation will be done for grade 3 AEs.

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events is requested by System Organ Class and preferred terms and according to occurrence of each event. For this purpose, the following additional analysis will be produced:

- The number of occurrences of non-serious solicited and unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination.
- The number of occurrences of SAE classified by the MedDRA Preferred Terms and reported from first vaccination up to study conclusion.

6.5.2.3. Pregnancies:

In case of any pregnancy from visit 1 (first vaccination) up to entire study duration, pregnancy reports and outcomes will be reported.

6.5.2.4. Clinical Safety Laboratory Investigations

Haematology profile, including differential cell counts is performed only at visit 1, before vaccination, and it will be summarized as baseline characteristics (see section 6.1.2) via descriptive statics. For each parameter: N, mean, median, SD, min and max will be computed and the frequencies of subjects with values above or higher normal ranges by treatment group.

6.5.2.5. Concomitant Medication

This analysis will consider all medications taken (and reported) for different purpose then COPD or AECOPD. The analysis of medications to treat COPD or AECOPD (standard of care and not standard of care) is described in section 6.6.2.

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects starting/reporting concomitant medications within the 7-day follow-up period (day 1 – day 7), during the 30-day follow-up period (day 1 – day 30) post-vaccination and during the entire study period will be tabulated by vaccine group for each study dose and across doses.

6.6. Other Analysis

6.6.1. Microbiological assessment

6.6.1.1. Sputum sample collection and quality

Sputum sample collection

Patient sputum sample will be collected (as stable visit) at Day 1 (before vaccination) and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD driven visit, where AECOPD is confirmed.

Within each vaccine group the percentage of patients at each study visit (stable visit) and AECOPD confirmed visit will be computed overall and by the method (i.e., spontaneous at study visit or spontaneous at patient's home, induced using 0.9% saline or induced using 3% saline).

The proportion of sputum samples obtained at overall and at each stable and AECOPD visits and positive for specific bacterial pathogens by bacteriological culture and PCR will be computed, by vaccine group.

Sputum sample quality

The quality of sputum is assessed via squamous cells count, neutrophils cells count and bacteria direct smear. These will be summarized at any sputum visit (stable) and at any AECOPD confirmed visit, via frequencies tables (i.e., frequencies of sputum samples per quality scores [see section 11.2.7 in Annex 1] within each vaccine group)

If more than 20% of sputum samples have bad quality the analyses of bacteriological efficacy endpoint and bacteriological load (via PCR and culture) will be repeated in the subset of sputum samples with good and moderate quality.

6.6.1.2. Sputum bacterial/viral results via qPCR

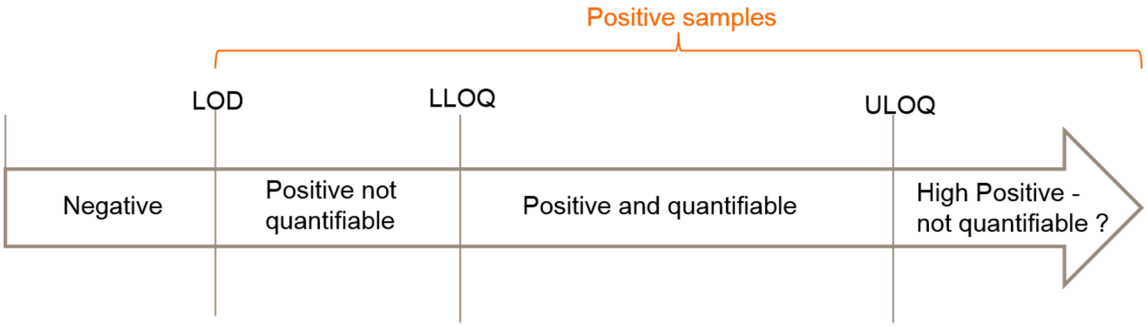
Identification and quantification of the*, H. influenzae (Hi), M. catarrhalis (Mcat) and S. pneumoniae (Pn) bacteria* on frozen sputum samples will be performed using quantitative PCR (qPCR).

Testing results will be released as copies/mL values from 0 copies/mL up to the highest value.

Positivity cut-off (LOD – limit of detection): Samples with results below the positivity cut-off are negative. Samples with results equal to or above the LOD (equal to 1561, 927 and 1161 Copies/mL for Hi, Mcat and Pn respectively) are positive.

Limits of quantification (Lower (LLOQ) and Upper (ULOQ)): Only samples with results between the LLOQ and ULOQ are quantifiable. Nevertheless, as it is not needed to work with precise value, samples with results above the ULOQ and below LLOQ will be included in the quantitative analysis.

Figure 2 Sputum sample positivity by qPCR



For the occurrence, presence, acquisition and apparition analysis a sample will be considered positive (to Hi, or Mcat or PN) if the qPCR results ≥ LOD.

Load analysis will be performed for Hi, Mcat and Pn considering sputum samples with qPCR load above or equal to (≥) the LOD, including the values belonging to the "not quantifiable" zone that will be anyway released by the assay (between LOD and LOQ, greater than ULOQ).

Occurrence and load of Hi and/or Mcat.

For each vaccine group the following analysis will be presented for sputum sample analysed via PCR:

- Overall proportion of sputum samples positive for Hi and Mcat with associated 95% CIs before vaccination (Day 1) and at any stable visit (Day 91, Day 181, Day 271, Day 361, Day 451) Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit
- Proportion of patients with sputum samples positive for Hi and Mcat with associated 95% confidence intervals (CIs), at each stable visit and at each AECOPD visit confirming acute exacerbation
- Summary statistics (N, mean, SD, median, minimum and maximum) and 95% CIs for the Hi and Mcat load will be displayed at each stable visit and at each AECOPD visit.

For the overall proportion, estimate and confidence intervals will be computed using a Generalized Estimating Equations (GEE) model assuming a binomial distribution for the response variable with logit as link function and a compound symmetry correlation matrix (exchangeable structure) to account for the within-patient correlations [Liang, 1986] and the following SAS code will be applied for stable visits, AECOPD visits separately and for Hi and Mcat bacteria:

```
PROC GENMOD data=<dataset> descending;
CLASS pid trt;
BY bacteria;
MODEL sp_positive = trt / dist = bin LINK = logit lrci ;
REPEATED subject=pid/ type=exch PRINTMLE;
ODS OUTPUT ParameterEstimates=out_parm ClassLevels=Class;
RUN;

DATA result;
 SET out_parm(where=(parameter='Intercept') drop=ChiSq ProbChiSq DF);
 format percent LL UL percent8.1;
      Percent=exp(estimate)/(1+exp(estimate));
      LL=exp(LowerLRCL)/(1+exp(LowerLRCL));
      UL=exp(UpperLRCL)/(1+exp(UpperLRCL));
      unit=_N_;
RUN;
```

where:

pid: patient id
trt= treatment arm;
sp_positive=sputum sample positive to bacteria (Hi or Mcat)

Acquisition and apparition of Hi and Mcat

The following definitions will be used (see Section 11.2.7 for further details):

Acquisition: The first time a bacterium is detected in the sputum of a patient over the course of the study visits (a positive status at the visit considered as baseline excludes a subject from this analysis).

Apparition: Detection of a bacterium in the sputum of a patient taken during a study visit which was not detected in the sputum taken during the previous visit

The following analyses will be performed for Hi (alone or with other bacteria), Mcat (alone or with other bacteria) and either Hi or Mcat:

- Percentages of subjects with acquisition for each treatment group and risk ratio between groups, considering both Day 1 and Day 91 as baseline.
- Percentages of subjects with apparition for each treatment group and risk ratio between groups, considering Day 1 as baseline.
- Percentages of subjects with acquisition at AECOPD visit for each treatment group and risk ratio between groups, considering both Day 1 and Day 91 as baseline.
- Percentages of subjects with apparition at AECOPD visit (when negative at previous stable visit) for each treatment group and risk ratio between groups, considering Day 1 as baseline
- Frequency table for apparition (number of apparitions for each subject from Day 1), by treatment groups.

Other bacteriological/viral pathogens

In addition to proportion of sputum positive to Hi (*Haemophilus influenza)* and Mcat (*Moraxella catarrhalis)* also the proportion of sputum samples obtained from PCR at pre-vaccination (Day 1), at Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit that are positive for specific bacteria (such as *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and *Streptococcus pyogenes* [*S. pyogenes*]) and virus (such as *respiratory* syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) will be presented together with the 95% CIs.

For the *S. pneumonia* and Rhinovirus summary statistics (N, mean, SD, median, minimum and maximum) and 95% CIs for the load will also be tabulated.

6.6.1.3. Sputum bacterial results via culture

In the subset of subjects from whom the sputum will be analysed also by culture, the proportion of subjects with sputum sample positive and the number and proportion of sputum sample positive to Hi/NTHi (with or without the *H. influenzae* confirmation by PCR of the collected bacterial isolates) and Mcat by culture will be displayed at each stable visit and at each AECOPD visit together with the 95% CIs, within each treatment group, using the same method as for PCR.

Frequencies of semi-quantitative bacteriological load (few scattered, +, ++, +++), for each vaccine group will be tabulated.

The following analyses will be performed for NTHi (alone or with other bacteria), Mcat (alone or with other bacteria) and either Hi or Mcat detected by culture:

- Percentages of subjects with acquisition for each treatment group and risk ratio between groups, considering both Day 1 and Day 91 as baseline.

- Percentages of subjects with apparition for each treatment group and risk ratio between groups, considering Day 1 as baseline.
- Percentages of subjects with acquisition at AECOPD visit for each treatment group and risk ratio between groups, considering both Day 1 and Day 91 as baseline.
- Percentages of subjects with apparition at AECOPD visit (when negative at previous stable visit) for each treatment group and risk ratio between groups, considering Day 1 as baseline
- Frequency table for apparition (number of apparitions for each subject from Day 1), by treatment groups.

Other bacteriological pathogens

In addition to proportion of sputum positive to Hi (*H. influenza)* and Mcat (*M. catarrhalis)*, also the proportion of sputum samples at pre-vaccination (Day 1), at Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit that are positive to *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and other bacteria identified via culture, will be presented together with the 95% CIs.

6.6.2. Health related quality of life (QOL)

The following analysis are exploratory and a p-value <0.1 will be considered statistically significant, however 2-sided 95% CIs will be computed to show precision of estimation. All comparisons should be interpreted with caution considering that there will be no adjustment for multiplicity.

For each of the following questionnaire missing items will not be imputed and subjects with partial data will be excluded.

EXACT-PRO daily score

The EXAcerbations of Chronic pulmonary disease Tool (EXACT) constitutes of 14 items which are patient-reported outcome (PRO) via daily diary.

All EXACT-pro scores will be divided in to the following periods:

- Screening: scores collected between screening and Visit 1 (Baseline)
- Treatment: scores collected between Visit 1 and Visit 4 (i.e., 1 month post-Dose 2)
- Exacerbation: scores collected during the start date of an exacerbation until resolution.
- Follow –up: scores collected between Visit 4 (1 month post-Dose 2) until study completion (one year after - Visit 8).
- Follow-up will be also divided by 3 months sub period:
  - from Visit 4 to Visit 5 (Day 91 to Day 180)
  - from Visit 5 to Visit 6 (Day 181 to Day 270)

- from Visit 6 to Visit 7 (Day 271 to Day 360)
- from Visit 7 to Visit 8 (Day 361 to Day 450)

Descriptive statistics

For each subject the average score across all days, within each period is computed. The mean score will be reported as descriptive statistics within each group (i.e., vaccine and placebo). N, mean, SD, median, min and max, on the **EXACT-PRO** average scores will be tabulated during all (stable) periods and during exacerbations.

Between groups comparison

At each period and sub period the two groups will be compared using an ANCOVA model, with the baseline value (i.e., score at screening) as covariate and treatment as fixed factor.

Note: EXACT-PRO baseline score at screening will be computed as the average within-patient score collected between screening Visit and Visit 1. If fewer than 4 days scores are available, the EXACT-PRO baseline score cannot be calculated, and it will result as missing.

COPD Assessment Test (CAT)

COPD Assessment test (CAT) is a patient-completed questionnaire assessing globally the impact of COPD (cough, sputum, dyspnoea, chest tightness) on health status. It constitutes of 8 items each scoring from 1 to 5. The Total score is given by the sum of the single item scores and it ranges from 0 to 40. Higher scores denote a more severe impact of COPD on patient's life.

CAT questionnaire will be provided to all enrolled patients at Screening, Day 271 and Day 451 (end of study), and at each AECOPD visit.

Descriptive statistics

Descriptive statistics (N, mean, SD, median, Q1 and Q3, min and max) on the CAT total score (obtained as sum of the scores of 8 single items) will be reported by scheduled visits (stable visits), by AECOPD visit and by each treatment group.

Data will be also represented via line-chart for the total score at each time points (screening, Day 271, Day 415 and any AECOPD visit) together with the 95% confidence interval around the mean of the total score.

Within group change and CAT responders.

For each group and at each time point (Screening, Day 271 and Day 421), the mean of total score together with SD will be reported and a pair t-test will be performed to compare screening scores with scores at Day 271 and at Day 421.

Moreover, the percentage of "CAT responder" subjects will be calculated at Day 271 and 421. A "CAT responder" is defined as a subject with at least a 2 units improvement (Decrease in total score) with respect to the baseline (Screening)

Between groups comparison

Differences between groups will be analysed in terms of difference in mean for each time points (Day 271 and Day 421) by one-way ANOVA model on the total scores, with vaccine group as factor.

CAT Score at AECOPD Visit

N, mean, SD, median, Q1 and Q3, min and max CAT score during AECOPD visit will be displayed according to the number and severity of AECOPD event.

St. George's Respiratory Questionnaire assessment (SGRQ-C)

The St. George's Respiratory Questionnaire (SGRQ) is composed of 76 items that are weighted to produce three component scores: Symptoms: measuring distress caused by respiratory symptoms, Activity: measuring the effect of difficulties in mobility and physical activity, and Impact: quantifying the psychosocial impact of the disease.

A "Total" score is also computed as sum from all component items score, thus providing a global estimation of the patients respiratory health. Each of these scores ranges from 0 to 100, a score of 100 indicating maximum disability [Jones, 1991]

SGRQ-C will be provided to all enrolled patients at Screening, Day 271 and Day 451 (end of study), and at each exacerbation visit.

Descriptive statistics

Descriptive statistics (N, mean, SD, median, Q1, Q3, min and max) on the SGRQ-C (total score and symptoms, activity and impacts component scores) will be reported by scheduled visits (stable visits), at each AECOPD visit and by each treatment group.

Mean score for each component (symptoms, activity and impacts) and mean total scores will be also represented via line-chart at each time points (screening, Day 271, Day 415 and any AECOPD visit) together with the 95% confidence interval around the mean.

Within group change and SRGQ-C responders.

For each group and at each time point (Screening, Day 271 and Day 421), the mean of each component score and the mean of total score together with SD will be reported and a pair t-test will be performed to compare screening scores with scores at Day 271 and at Day 421. Moreover, the percentage of "SRGQ-C responder" subjects will be calculated at Day 271 and 421. A "SRGQ-C responder" is defined as a subject with an improvement of more than 4 unit (Decrease in total score) with respect to the baseline (Screening).

Between groups comparison

For all components and for the total scores, differences between groups will be analysed in terms of difference in mean for each time points (Day 271 and Day 421) by one-way ANOVA model on the total scores, with vaccine group as factor.

SGRQ-C at AECOPD Visit

N, mean, SD, median, min and max, of each component scores and of total score during AECOPD visit will be displayed according to the number and severity of AECOPD event.

Use of medication to treat (AE)COPD and Healthcare utilization (HCU)

Frequency table on the number and type of healthcare utilisation (Physician's office, Visit to Urgent Care, Visit to Emergency Department, Hospitalization) during entire study period will be presented overall and by vaccine group.

Same frequency table will be also presented for two sub-periods: all HCU before 1-month after second vaccination and all HCU between 1-month after second vaccination and study end.

Frequency table on the use of medication for COPD (or AECOPD) and type (Chronic use for COPD, Chronic use for other disorders, exacerbation rescue medication) during entire study period will be presented overall and by vaccine group.

Medications will be coded using the GSKDRUG dictionary and frequencies table by GSKDRUG code will be also reported for entire study period, overall and by vaccine group.

As for HCU frequency tables will be presented also for the two sub-periods: before 1-month after second vaccination and after 1-month after second (until study completion).

6.6.3. Lung function and biomarkers

Pre- and post-bronchodilator spirometry

Pre- and post-bronchodilator spirometry assessments will be done at the Screening Visit (pre Day 1), Visit 6 (Day 271) and at Visit 8 (Day 451).

The following pulmonary function parameters will be evaluated:

- Forced Expiratory Volume in 1 second (L): **FEV_1**
- Forced Expiratory Volume in 1 second percent of predicted (%): **FEV_1PP**
- Forced Vital Capacity (L): **FVC**
- Forced Vital Capacity percent of predicted (%): **FVCPP**
- FEV_1 and FVC ratio: **FEV_1/FVC**

- Peak Expiratory Flow (L/sec): **PEF**
- Forced expiratory flow between 25% and 75% of FVC (L/sec): **$FEF_{25-75\%}$**
- FEF between 25-75% of FVC percent of predicted(%): **$FEF_{25-75\%}$PP**

Descriptive analysis (N, mean, SD, median, min and max) on all spirometric measurements at each time point.

Biomarkers

The following selected biomarkers will be evaluated at Day 1 and Day 451 and at each AECOPD visit: fibrinogen, hsCRP and IP-10.

Descriptive statistics (N, mean, SD, median, min and max) will be tabulated for each biomarker and at each time point.

6.6.4. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate humoral immune responses to vaccination and efficacy (i.e., reduction in AECOPD). Details of the methodologies will be included in ad hoc SAP for this purpose.

7. ANALYSIS INTERPRETATION

The primary objective analysis (efficacy) of this study will be evaluated at alpha error of 13% (two-sided test) which is the measurement of the accuracy of our estimation.

Also 2-sided 95% CIs will be provided to show the precision of estimation.

For the secondary objectives we have the following:

- Inferential analyses for primary analysis of efficacy are planned to be performed at alpha level of 0.13 (two sided). No alpha adjustment for multiple testing in the secondary endpoints will be performed, and only the 2-sided 95% CIs will be provided
- All other efficacy and immunogenicity analyses are planned to be performed at alpha level of 0.05 with no adjustment for multiplicity.

CMI and safety analyses are intended to be descriptively only.

All tertiary objectives are exploratory and a p-value <0.1 is considered as reference for statistical significance in comparative analysis. Those comparisons should be interpreted with caution.

8. CONDUCT OF ANALYSES

The analysis planned in this study will be performed in four steps giving higher priority to the most relevant objectives (i.e., primary, secondary)

Specifically, the analyses will be released in this order:

- Priority 1 analyses will be released at first and reported in a full clinical study report (CSR), this analysis is performed in to two steps:
  - Step 1: Analysis of primary efficacy endpoint and secondary safety endpoint.
  - Step 2: Analysis of immunogenicity, CMI and bacteriological PCR secondary endpoints plus the following tertiary objectives:
    - To evaluate the effect of the investigational vaccine on the presence and load of NTHi and/or Mcat at stable visits and AECOPD by PCR.
    - To explore the impact of the investigational vaccine on health-related quality of life (HRQOL).
    - To explore the T helper profile of the PD-, PE-, PilA-, UspA2-specific CD4+/ CD8+ T cell responses
- Priority 2 analysis will be released in a third step and reported in to an Annex report. They include, the following tertiary objectives:
  - *To evaluate the effect of the investigational vaccine on the presence, acquisition/apparition and load of NTHi and/or Mcat at stable visits and AECOPD by culture.*
  - *To evaluate the effect of the investigational vaccine on the presence, acquisition/apparition and load of NTHi and/or Mcat at stable visits and AECOPD by culture. To explore the efficacy of the investigational vaccine as compared to placebo with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe) associated with NTHi and/or Mcat detected in a subset of sputum samples by culture.*
  - *To explore the impact of the investigational vaccine on use of medication for COPD and Healthcare Resource Utilization.*
  - *To explore the impact of the investigational vaccine on lung function.*
  - *To describe selected biomarkers in stable COPD and during AECOPD*

  and other stratified analyses to evaluate VE in subsets:
    - Vaccine efficacy (clinical and bacteriological) by eosinophil level in blood at baseline
    - Vaccine efficacy (clinical and bacteriological) by NTHi presence in sputum (detected by PCR) at baseline
    - Vaccine efficacy (clinical and bacteriological) by Mcat presence in sputum (detected by PCR) at baseline

  - Vaccine efficacy (clinical and bacteriological) by NTHi or Mcat presence in sputum (detected by PCR) at baseline

- Priority 3, analyses will be release in a fourth step and reported in an Annex or technical report (if related to assay development) and they include the following tertiary objectives:

  – *To collect blood and sputum samples for assay development, for lung microbiome analysis, to explore the level of inflammation (into the lung) and/ or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.*

  – *To explore the data for an immune correlate of protection*

  And additional request for EXACT event analysis

In addition to the data and analysis for the clinical study report, four safety interim data evaluations will be carried by an internal Safety Review Committee (iSRC).

8.1. Sequence of analyses

The following safety interim analyses performed by iSRC are planned:

First one will be done once 60 subjects complete one month after first vaccination (i.e., the first 60 subjects completed Visit 2-Day 31)

Second one will be done once 60 subjects complete one month after second vaccination (i.e., the first 60 subjects completed Visit 4- Day 91)

Third one will be done once 300 subjects complete one month after first vaccination (i.e., the first 300 subjects completed Visit 2- Day 31)

Fourth one will be done once 300 subjects complete one month after second vaccination (i.e., the first 300 subjects completed Visit 4- Day 91)

Table 9 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
60 subj safety post dose 1	E1_02	Internal	N	N	See SRT column in TOC
60 subj safety post dose 2	E1_03	Internal	N	N	See SRT column in TOC
300 subj safety post dose 1	E1_04	Internal	N	N	See SRT column in TOC
300 subj safety post dose 2	E1_05	Internal	N	N	See SRT column in TOC
All data analysis	E1_01	Study report	Y	Y	All tables in final TOC

8.2. Statistical considerations for interim analyses

Four (unblinded) interim analyses to evaluate the safety during the exposure period will be conducted. These analyses will be performed by an internal Safety Review Committee (iSRC) and study team will not be part of the vaccine unblinded review of safety data.

The iSRC will conduct *unblinded* reviews of all available safety data from the present study while taking into account any other findings that could have an impact on the safety of the subjects and will determine whether there is a safety signal that needs to be escalated to GSK Biologicals' Vaccines Safety Monitoring Board (VSMB). In the event that a safety signal is observed, GSK Biologicals' VSMB might decide to suspend, modify or continue the conduct of the study.

Before each iSRC safety evaluation in this study, the SRT will review the same safety data, but in a ***blinded*** manner.

In addition to the planned iSRC (and SRT) evaluations, *ad hoc* safety evaluations can take place if a safety concern is identified by an investigator or by the SRT.

Interim analysis unblinded data will not be circulated outside of the iSRC team and no individual clinical study report will be written as a result of these safety evaluations.

The planned interim analyses are only for safety monitoring. No conclusions on efficacy, immunogenicity or other endpoints will be carried out, thus no alpha adjustment will be performed.

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, 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.

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

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Handling missing efficacy data:

Efficacy – Clinical Endpoint

Missing or non-evaluable measurements will not be replaced.

For subjects who withdrawn before follow up completion, the AECOPD rate will be reproportioned, only for the purpose of the descriptive summary tables, as follow: the AECOPD rate is calculated proportionally to the actual follow-up time (number of events/number of days observed) and then scaled to the period considered (i.e., before 1 month post Dose 2 =90 days, after 1 month post Dose 2 = 365 days)

Efficacy – Bacteriological Endpoint

For a given subject and a given bacteriological measurement, missing or unevaluable measurements will not be imputed.

Subjects who did not have any sputum collected or have missing measurements at all AECOPD (if at least 1 AECOPD occurred) will not be taken into account for the NTHi and/or Mcat-associated AECOPD analyses.

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. 1934].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the paper from Robert G. Newcombe [Newcombe, 1985]: interval estimation for the difference between independent proportions: comparison of eleven methods. The standardised asymptotic method used is the method six.

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 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 1 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.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which injection occurred. More specifically dose 1 refers to all injections administered at the first vaccination visit (Visit 1) while dose 2 corresponds to all injections administered at the second vaccination visit (Visit 3) 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.
- The number of doses for a product is the number of time the product is 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 Kilogramm= weight in Pounds / 2.2
  - Weight in Kilogramm =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 (ie 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

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)

- Exacerbations in previous 12 months

Data will be categorized as following:

1. AECOPDs in the last 12 months managed without oral corticosteroids and antibiotics =’Mild’
2. AECOPDs in the last 12 months that required oral corticosteroids and/or antibiotics =’Moderate’
3. AECOPDs in the last 12 months that required hospitalization=’Severe’

11.2.4. Efficacy

- **AECOPD events**: AECOPD events are confirmed according to investigator judgment after an AECOPD visit which is aimed to exclude worsening in symptoms not related to an AECOPD event.

eDiary alerts refer to daily symptoms recorded the morning after (also called morning symptoms). Alerts are based on the Anthonisen criteria:

- Worsening of two or more of the following major symptoms for at least two consecutive days*: dyspnea, sputum volume, sputum purulence (color)

  Or

- Worsening of any major symptom together with any of the following minor symptoms for at least two consecutive days*: sore throat, cold (nasal discharge and/or nasal congestion), fever (oral temperature ≥ 37.5°C) without other cause, increased cough, increased wheeze.

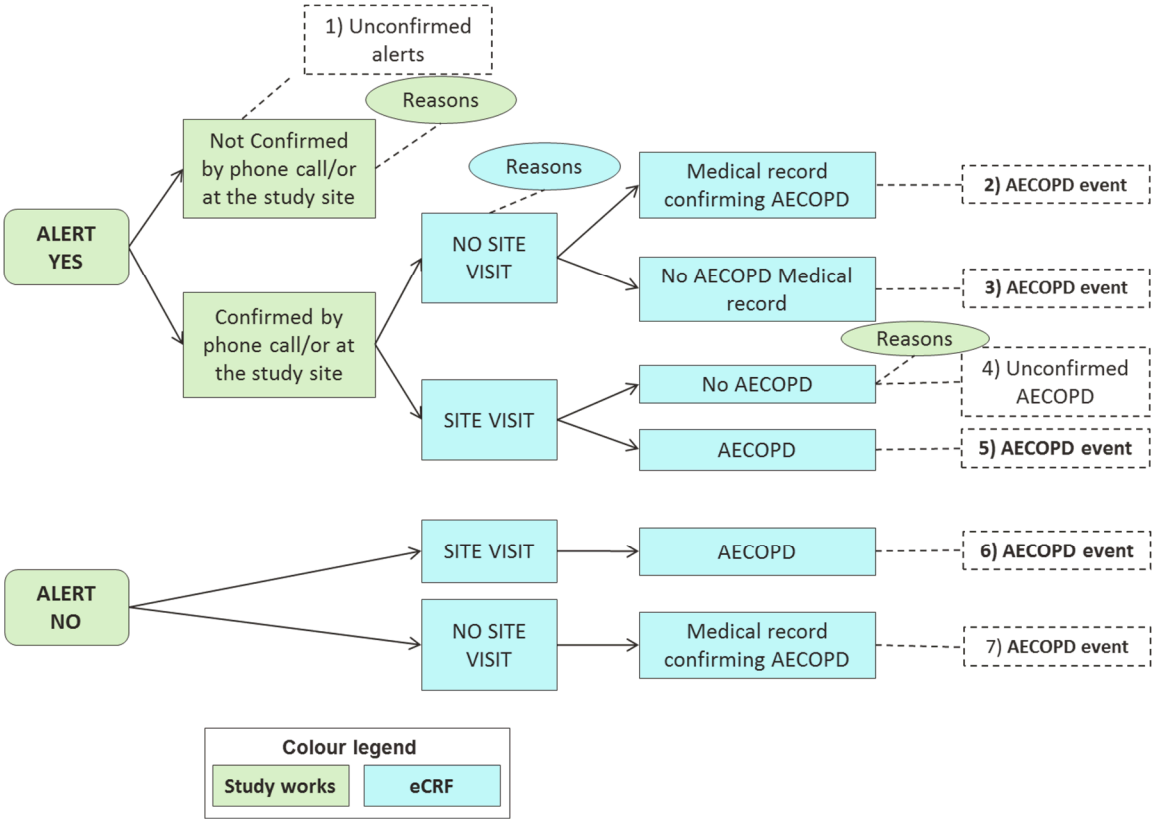
** The same two symptoms do not have to be present on both days as long as at least one major symptom is present on both days.*

AECOPD visits are scheduled after an electronic Diary Card alert confirmed by the investigator (by phone call or at the study site) or after spontaneous site visits due to worsening symptoms without any alert.

Potential AECOPD will be confirmed and registered as AECOPD event based on the following scheme:

- eDiary ALERT + phone call no confirmed = NO AECOPD event
- eDiary ALERT + phone call confirmed + site visit confirmed = AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no confirmed = NO AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no performed + Medical record confirmed = AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no performed + Medical record no confirmed = NO AECOPD event.
- eDiary ALERT + phone call confirmed + site visit NO performed + Medical record no available = AECOPD event.
- eDiary NO ALERT + site visit NO confirmed = NO AECOPD event.
- eDiary NO ALERT + site visit confirmed = AECOPD event.
- eDiary NO ALERT + site visit NO performed + Medical record confirmed = AECOPD event.
- eDiary NO ALERT + site visit NO performed + Medical record no available/no confirmed = NO AECOPD event

Figure 3 AECOPD assessment*



**Only AECOPD confirmed by the Investigator and reported in eCRF will be counted for efficacy analysis.*

- **AECOPD onset date**: AECOPD onset is defined as the first day of the two consecutive days of worsening symptoms and it entered in e-CRF by the investigator.
- **AECOPD recovery date:** AECOPD recovery will be determined / confirmed by the investigator during (a) follow-up phone call(s) which will take place every 2 weeks until the AECOPD has resolved. The end date should be based on when the investigator and/or subject determines that the AECOPD symptoms have returned to pre-exacerbation levels or to a new baseline. In determining this end date, consideration will be given to symptoms recorded in the electronic Diary Card and patient assessment during the phone calls.
- **AECOPD duration** will be defined as the number of days from AECOPD onset (included) and AECOPD recovery (not included).

  Duration = date2 – date1,

  with date2: AECOPD recovery date,

  date1: AECOPD onset date
- **Unconfirmed AECOPD event with morning e-diary signal alert notification:** An alert from the electronic Diary Card not confirmed to be an AECOPD after contact by phone call or at the study site.

- **Grading of severity of an exacerbation:** Severity of exacerbations is defined as per protocol:
  - Mild: Worsening symptoms of COPD that are self-managed by the patient.
  - Moderate: Worsening symptoms of COPD that require treatment with oral corticosteroids and/or antibiotics.
  - Severe: Worsening symptoms of COPD that require treatment with in-patient hospitalisation or home care intervention.

Severity of the exacerbation will not be derived but taken directly from the information entered in the CRF (i.e. Severity of exacerbation will be taken from the conclusion of the exacerbation visit).

11.2.5. 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 titre transformations. Antibody titres 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 GMT calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol (see also Table 2 on section 6.4.1 of SAP).
- 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 titre is greater than or equal to 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.
- 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 a value < cut_off, numeric result = cut_off/2,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - else numeric result is left blank.

11.2.6. 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 adverse events within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited adverse events based on the Total Vaccinated Cohort (TVC) 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.
- All solicited adverse events will be considered probably related to study vaccine.

Unsolicited adverse events: 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 adverse event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

- Unsolicited AE will be classified in the e-CRF as possibly related to study vaccine (YES or NO), based on the PI judgment.
- The related dose for an event (e.g., AE, medication, vaccination,…) is the study dose given before an event. In case the event takes place on a day a study dose is given, the related dose will be that of the study dose even if the event actually took place before. For instance, for a conc. medication started on the day of study dose 2 but before dose 2 administrations, the related dose will be dose 2.

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.

Table 10 Denominator for safety tables

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Solicited general adverse event	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 adverse event	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 adverse event	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
Concomitant vaccination	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.

Table 11 Number of decimals per parameter

Parameters	Number of decimal digits
% of count, including LL & UL of CI	1
p-value	3
Mean, median	Number of decimals in the raw data + 1
SD	Number of decimals in the raw data + 2
Minimum, maximum, range	Number of decimals in the raw data

LL = Lower Limit UL = Upper Limit CI = Confidence Interval
SD = Standard deviation

11.2.7. Other endpoints

Acquisition and apparition of NTHi and Mcat

For the purpose of the analysis the following definitions are to be used:

1. Acquisition: the first time a bacterium is detected in the sputum of a patient over the course of study visits (bacterium presence at first study visit is not considered acquisition); either stable or exacerbation visits are considered.
2. Apparition: detection of a bacterium in the sputum of a patient taken during a study visit which was not detected in the sputum taken during the previous visit; either stable or exacerbation visits are considered.
3. No acquisition: a visit at which a bacterium is not detected in the sputum or a visit that follows an acquisition; first study visit is not considered. either stable or exacerbation visits are considered.
4. No apparition: a visit at which a bacterium is not detected in the sputum or a visit at which a bacterium is detected but not preceded by a negative visit

Note: in qPCR acquisition and apparition a bacterium detected means the qPCR results ≥ LOD.

Sputum quality criteria

Quality of sputum is define using the following criteria and based on squamous cells count in fresh sputum [Geckler, 1977]:

- >25 squamous epithelial cells/field → sample of bad quality
- 10-25 squamous epithelial cells/field →sample of moderate quality
- < 10 squamous epithelial cells/field → sample of good quality

Computation of the final HRV status

The final HRV status takes into account data coming from both the Allplex assay and HRV RT-qPCR assay. A new variable for the final postivitiy/negativity (qualitative results) of HRV, for each sample, will be computed based on the below combination:

Allplex HRV result	Allplex HEV result	HRV RT-qPCR	Final HRV result (variable to be created)
POSITIVE	NEGATIVE	*Any results*	POSITIVE
	POSITIVE	*Any results*	
NEGATIVE	POSITIVE	IR	NEGATIVE
		NFR	
		RBSA	
		< LOD	
	POSITIVE	≥ LOD	POSITIVE
	NEGATIVE	Not tested	NEGATIVE

HRV= Human Rhino-Virus
HEV= Human Entero-Virus
IR = Invalid Result
NFR = No Final Result
RBSA = Rejected because of sample anomaly
LOD = Limit of Detection

11.3. Randomization method and minimization algorithm

Subjects are randomised using a centralised randomisation system on internet (SBIR) at first dose. The system incorporates a minimization alogorithm based on White SJ and Freedam LS method [White SJ, Freedman LS, 1978] and it is described below:

Notation:

- k input values to be used for minimization, each with a weight w_k (k=1,.., K) and l_k variants.
- i treatment groups applicable to stratum the subject has been identified with randomization ratio a_1,… a_i
- D: percentage of determinism
- W: weight assigned to each minimization factor

In this study k=4: Country, GOLD grade, History of exacerbation and Age group defined as :

COUNTRY [8 variants]: BE CA FR DE IT ES UK US

GOLD [3 variants]: 2 3 4

AGECAT [2 variants]: 40-60 61-80

HIST_ES [2 variants]: < 2 >=2

i=2: VACCINE and PLACEBO with randomization ratio 1:1 (a_i=1)

D=90%

W=1 for each variable

Algorithm:

For a new subject in criteria levels $s_1 \ldots s_k$

Step 1: Minimization computation

Step 1.1: Initialize Problem flag to 0

For each criteria variants s_k, compute the number of subjects already enrolled in each treatment within the strata dedicated to the subject.

Let b_{ik} the number for treatment i & criteria variant k: b_{ik} is the total number of subjects already randomized in treatment i and in criteria variant k within the strata dedicated to the subject.

Step 1.2: For each treatment i: compute Ai = 1/ai * sumk(w_k*b_{ik})

Step 2: determine whether the algorithm is random or determinist:

Generate R, a random number within [0-1], uniform distribution

Step 3: check determinism

If R < % determinism, go to step 4 (determinism) else go to step 5 (random)

Step 4: determinism

4.1: Identify all treatments with the lowest value Ai

4.2: Select randomly one of the treatments identified in step 4.1, let it be T. Go to step 6, if no more treatment then randomization failed

Step 5: randomization

Select randomly one of the treatments dedicated to subject's strata, let it be T. Go to step 6, if no more treatment then randomization failed.

Step 6: treatment allocation

Assign one of the treatment number. related to treatment T in the subject's center.

If no treatment number. related to treatment T is available in the subjects center, then go & repeat step 4 (determinism) or 5 (random) while dropping treatment T (set problem flag=1).

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase IIB, randomised, observer-blind, placebo-controlled, multi-centre study to evaluate the efficacy, safety, reactogenicity and immunogenicity of the GSK Biologicals' investigational vaccine GSK3277511A when administered intramuscularly according to a 0, 2 months schedule in COPD patients aged 40 to 80 years with a previous history of acute exacerbation (AECOPD).
eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
Scope:	All analyses for the final clinical study report
Date of Statistical Analysis Plan	Final v2: 13-Feb-2018
Co-ordinating author:	PPD (Lead Statistician)
Reviewed by:	PPD (Clinical Research & Development Lead) PPD (Director Clinical Statistics) PPD (Peer Reviewer Statistician) PPD (Lead Statistical Analyst) PPD (Scientific Writer) PPD (Regulatory Affair) PPD (SERM Physician) PPD (Public disclosure representative) PPD (Vaccine Developer Leader) PPD (Clinical read-out team Leader)
Approved by:	PPD (Clinical and Epidemiological Project Leader) PPD (Director Clinical Statistics) 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
AECOPD	Acute exacerbation of Chronic Obstructive Pulmonary Disease
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATP	According to Protocol
CI	Confidence Interval
BMI	Body Mass Index
CMI	Cell-mediated immunogenicity
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CSR	Clinical Study Report
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
EXACT-PRO	EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
HCU	Healthcare utilisation
HRQOL	Health-related quality of life
ICS	Intracellular cytokine staining
iSRC	Internal Safety Review Committee
ITT	Intent to treat
LL	Lower Limit of the confidence interval
Max	Maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MCAR	Missing Completed at Random

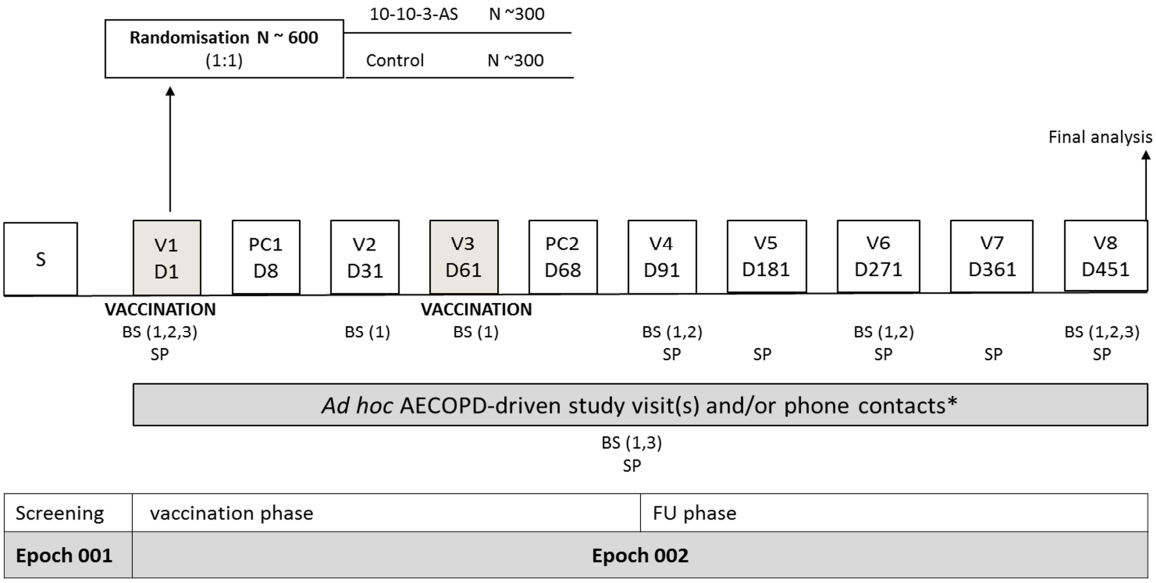
Min	Minimum value
mTVC	modified Total vaccinated cohort
PCR	Polymerase chain reaction
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SERM	Safety Evaluation & Risk Management
SOC	System Organ Class
SRT	Safety review team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated cohort
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
26-OCT-2017	First Version	Final Version 2: 07 June 2017
13-FEB-2018	Amendment 1 To align with the changes in the Protocol Amendment	Amendment 1 Final: 30 Nov 2017

2. STUDY DESIGN

Figure 1 Study design overview



S = Screening Visit; **V** = Visit; **PC** = Phone contact; **D** = Day; **FU** = Follow-up; **BS (1)** = blood sample for humoral immunogenicity; **BS (2)** = blood sample for cell-mediated immunogenicity (CMI), this blood sample will only be collected from a sub-cohort of subjects; **BS (3)** blood sample for biomarkers; **SP** = sputum sample
The allowed maximum interval between Screening Visit and Visit 1 is 29 days. If a delay occurs for an eligible subject so that the interval exceeds 29 days, some study procedures performed during the Screening Visit needs to be repeated repeated within 7 days (see Table 6 of the protocol for more details).
* An AECOPD visit should be scheduled as soon as possible after the onset of AECOPD symptoms (max 96 hours after and, if applicable, preferably before starting treatment with antibiotics).During this visit blood and sputum samples will be collected. In addition, follow-up phone call(s) and/or visit(s) will take place to determine the end of the AECOPD. These contacts will take place at least every 2 weeks until the AECOPD is resolved.

Investigational vaccine and placebo will be administered in addition to standard of care.

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

Duration of the study: for each subject enrolled, the study will last approximately 15 months from Visit 1 up to study completion (Visit 8).

- Epoch 001: Screening Visit (Day -28 to Day -1).
- Epoch 002 : Primary starting at Visit 1 (Day 1) and ending at Visit 8 (Day 451).

Primary completion Date (PCD): Last Subject Last Visit (LSLV) from Visit 8 (Day 451) or last visit/contact of Epoch 002.

Study groups:

- **10-10-3-AS**: Approximately 300 subjects receiving two 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.
- **CONTROL**: Approximately 300 subjects receiving two doses of placebo (PBS).

The following group names will be used for the statistical analysis

Table 1 Study groups and epochs foreseen in the study

Group order in tables	Number of subjects	Group label in tables	Group definition for footnote
1	~300	10-10-3-AS	2 doses of AS01E-adjuvanted NTHI/Mcat vaccine containing 10 mcg of PD, PE-PilA and 3 mcg of UspA2
2	~300	PLACEBO	2 doses of phosphate buffered solution

Sampling schedule:

- **Blood samples for assessment of humoral immunogenicity** will be collected from all subjects at Visit 1 (Day 1), Visit 2 (Day 31), Visit 3 (Day 61), Visit 4 (Day 91), Visit 6 (Day 271), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
- **Blood samples for assessment of cell-mediated immunogenicity (CMI)** will be collected from all subjects in the CMI sub-cohort (approximately 60 subjects in each group) at Visit 1 (Day 1), Visit 4 (Day 91), Visit 6 (Day 271) and at Visit 8 (Day 451).
- **Blood samples for biomarkers** will be collected from all subjects at Visit 1 (Day 1), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
- **Blood sample for haematology profile** will only be collected at Visit 1.
- **Sputum samples for PCR** (all subjects) **and culture** (50% of subjects) will be collected from all subjects at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 271), Visit 7 (Day 361), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.

Other assessments:

COPD symptoms: All subjects will be asked to record COPD symptoms in their electronic Diary Card:

- Daily in the morning throughout the study (including during AECOPD): **morning symptoms questionnaire**.

- Daily in the evening throughout the study (including during AECOPD): **EXACT-PRO questionnaire**.

HRQOL assessments:

- All subjects will be asked to complete the COPD assessment test (CAT) at the Screening Visit (pre-Day 1), Visit 6 (Day 271), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
- All subjects will be asked to complete St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) at the Screening Visit (pre-Day 1), Visit 6 (Day 271), at Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.

Pre- and post-bronchodilator spirometry assessments will be done for all subjects at the Screening Visit (pre-Day 1), Visit 6 (Day 271) and at Visit 8 (Day 451).

3. OBJECTIVES

3.1. Primary objective

- To assess efficacy of the investigational vaccine as compared to the placebo control with respect to the rate of moderate and severe AECOPDs.

3.2. Secondary objectives

- To describe the safety and reactogenicity of the investigational vaccine.
- To assess efficacy of the investigational vaccine as compared to the placebo control with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe).
- To assess efficacy of the investigational vaccine as compared to placebo with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe) associated with NTHi and/or Mcat detected by PCR.
- To evaluate the humoral immunogenicity of the investigational vaccine.
- To evaluate the cellular immunogenicity of the investigational vaccine.

3.3. Tertiary objectives

- To evaluate the effect of the investigational vaccine on the presence and load of NTHi and/or Mcat at stable visits and AECOPD by PCR.
- To evaluate the effect of the investigational vaccine on the presence and load of NTHi and/or Mcat at stable visits and AECOPD in a subset of sputum samples by culture.
- To explore the efficacy of the investigational vaccine as compared to placebo with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe) associated with NTHi and/or Mcat detected in a subset of sputum samples by culture.

- To explore the impact of the investigational vaccine on health-related quality of life (HRQOL).
- To explore the impact of the investigational vaccine on use of medication for COPD and Healthcare Resource Utilisation.
- To explore the impact of the investigational vaccine on lung function.
- To describe selected biomarkers in stable COPD and during AECOPD.
- To explore the T helper profile of the PD-, PE-, PilA-, UspA2-specific $CD4^+$/ $CD8^+$ T cell responses.
- To collect blood and sputum samples for assay development, for lung microbiome analysis, to explore the level of inflammation (into the lung) and/ or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.
- To explore the data for an immune correlate of protection.

4. ENDPOINTS

4.1. Primary endpoint

- Rate of moderate and severe AECOPD (any cause), occurring within a period starting 1 month post-Dose 2 and lasting for 1 year.

4.2. Secondary endpoints

Safety:

- Occurrence of each solicited local AE, during the 7-day follow-up period (Day 1 - Day 7) following each vaccination.
- Occurrence of each solicited general AE, during the 7-day follow-up period (Day 1 - Day 7) following each vaccination.
- Occurrence of any unsolicited AE, during the 30-day follow-up period (Day 1 - Day 30) following each vaccination.
- Occurrence of any pIMD from first vaccination up to study conclusion.
- Occurrence of any SAE from first vaccination up to study conclusion.

Efficacy: All AECOPD

- Yearly rate of all AECOPD (any cause, any severity) starting 1 month post-Dose 2, in vaccinated and control subjects.
  - Rate of moderate and severe AECOPD cases in vaccinated and control subjects, during 3, 6 and 9 months observation starting 1 month post-Dose 2.
  - Rate of all AECOPD cases in vaccinated and control subjects, during 3, 6, 9 and 12 months observation starting 1 month post-Dose 2.

  - Rate of all AECOPD cases in vaccinated and control subjects, during 3, 6, 9 and 12 months observation starting 1 month post-Dose 2, by severity.

- Time to first moderate or severe AECOPD.
- Time to first AECOPD of any severity.
- Time to first AECOPD, by severity.
- Duration of moderate and severe AECOPDs.
- Duration of AECOPDs of any severity.
- Duration of AECOPDs, by severity.

Efficacy: AECOPD associated to bacteriological pathogens (PCR)

- Rate of NTHi-associated and/ or Mcat-associated moderate and severe AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year.
- Rate of NTHi-associated and/ or Mcat-associated any severity AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year.
- Rate of NTHi-associated and/ or Mcat-associated AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year, by severity.
- Time to first moderate or severe NTHi-associated and/ or Mcat-associated AECOPD.
- Time to first NTHi-associated and/or Mcat-associated AECOPD of any severity.
- Time to first NTHi-associated and/or Mcat-associated AECOPD, by severity.
- Duration of moderate and severe NTHi-associated and Mcat-associated AECOPD.
- Duration of NTHi-associated and/or Mcat-associated AECOPDs of any severity.
- Duration of NTHi-associated and/or Mcat-associated AECOPD, by severity.

Immunogenicity and CMI:

- Anti-PD, anti-PE, anti-PilA and anti-UspA2 total IgG antibody concentrations as measured by ELISA at Day 1, Day 31, Day 61, Day 91, Day 271 and at Day 451, in all subjects.

  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 271 and at Day 451, in a sub-cohort of subjects.

4.3. Tertiary endpoints

Sputum sample PCR:

- Occurrence (presence and absence) and bacterial load measured by PCR of NTHi and/or Mcat in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD visit.

Sputum sample culture:

- Occurrence (presence and absence) and semi-quantitative bacterial load measured in a subset of sputum sample by culture of NTHi and/or Mcat in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD visit.
- Rate of NTHi-associated and Mcat-associated, moderate and severe AECOPD.
- Rate of NTHi-associated and Mcat-associated any severity AECOPD.
- Rate of NTHi-associated and Mcat-associated AECOPD, by severity.
- Time to first moderate or severe NTHi-associated and/or Mcat-associated AECOPD.
- Time to first any NTHi-associated and rate Mcat-associated AECOPD.
- Time to first NTHi-associated and rate Mcat-associated AECOPD, by severity.
- Duration of each moderate and severe NTHi-associated and Mcat-associated AECOPD.
- Duration of NTHi-associated and/or Mcat-associated AECOPDs of any severity.
- Duration of NTHi-associated and/or Mcat-associated AECOPD, by severity.

QOL:

- Assessment of EXACT-PRO score, daily in the evening throughout the study, in all subjects.
- Assessment of CAT scores at Screening, Day 271 and Day 451, and from first vaccination to study conclusion for each AECOPD visit, in all subjects.
- Assessment of SGRQ-C score at Screening, Day 271 and Day 451, and from first vaccination to study conclusion for each AECOPD visit, in all subjects.
- Assessment of use of medication to treat (AE)COPD and healthcare utilization in all subjects throughout the study period.

Lung function:

- Assessment of FEV1% of predicted normal value at Screening, Day 271 and Day 451, in all subjects.

Biomarkers:

- Concentration of selected biomarkers (fibrinogen, hsCRP and IP-10), at Day 1 and Day 451, and for each AECOPD visit from first vaccination to study conclusion.

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 271 and Day 451

Assay development, microbiome analysis and lung inflammation:

- Presence of respiratory viral pathogens in sputum (including respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) at Day 1, Day 91, Day 181, Day 271, Day 361, Day 451 and at each AECOPD visit from first vaccination to study conclusion
- Presence and/or concentration of inflammatory cytokines in sputum at Day 1, Day 91, Day 181, Day 271, Day 361, Day 451 and at each AECOPD visit from first vaccination to study conclusion on a subset of samples

5. ANALYSIS SETS

5.1. Definition

All enrolled set: All subjects who will sign the inform consent and for whom a subject code is assigned

The following study cohorts will be evaluated.

5.1.1. All enrolled set

All subjects who will sign the inform consent and for whom a subject number is assigned.

5.1.2. Total vaccinated cohort

The total vaccinated cohort (TVC-also called Exposed Set-ES) will include all subjects with at least 1 documented study vaccine administration:

- A **safety** analysis based on the TVC/ES will include all subjects with at least one vaccine dose administered and who provided safety data.
- An **immunogenicity/CMI/efficacy** analysis based on the TVC will include all vaccinated subjects for whom immunogenicity/CMI/efficacy data are available.

Note that in subjects receiving only one dose the efficacy endpoint is the number of moderate or severe AECOPD (any cause), occurring during 12 months observation period.

The TVC analysis will be performed per treatment actually administered at Dose 1.

5.1.3. Modified total vaccinated cohort

The modified total vaccinated cohort (mTVC) will include all subjects with 2 documented study vaccine administrations with respect to the vaccine actually administered.

The primary efficacy analysis will be performed on the mTVC.

5.1.4. Full Analysis set (FAS)

The FAS will include all randomized subjects who will receive at least 1 vaccine administration. As per intention-to-treat (ITT) principle, a subject in the FAS will be analysed "as randomized" (i.e. according to the vaccine a subject was planned to receive irrespectively of his/her real exposure).

5.1.5. Per- protocol set for analysis of efficacy

The Per-Protocol Set (PPS) for analysis of efficacy will include all subjects in the TVC:

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule.
- Who received the study vaccine according to protocol procedures.
- Who did not received a medication/ product/ vaccine that may have an impact on the efficacy or bacteriological load.

  In addition for the Bacteriological efficacy endpoints:

- For whom the sputum sample results are available.

5.1.6. Per-protocol set for analysis of immunogenicity and CMI

The PPS cohort for immunogenicity/CMI will include all subjects in the TVC:

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule.
- 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 for immunogenicity/CMI
- Who did not present an intercurrent medical condition leading to elimination from the PPS analysis for immunogenicity/CMI.
- Who complied with the blood sample timings.
- For whom post-vaccination immunogenicity results are available.

Note 1 that each of the above reasons for exclusion will be evaluated for each strain and each time point and thus different strains and time points could present different numbers of observations (N).

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 (ES)

Code 100 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES (previous called TVC)

Code 1030.2 (2^{nd} dose of vaccine not administered at all) will be used to identify subjects eliminated by mTVC.

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

5.2.2.1. 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
1030.2	2^{nd} dose of 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)
2040	Administration of any medication forbidden by the protocol
2050	Developed a withdrawal criterion but was not withdrawn
2080	Subjects did not comply with vaccination schedule
2090.a	Subjects did not comply with blood sample schedule
2090.b	Subjects did not comply with sputum sample schedule
2100.a	Serological results not available post-vaccination
2100.b	Sputum results not available post-vaccination
2100.c	CMI results not available post-vaccination for those in CMI subset
2100.d	Blood Biomarker results not available post-vaccination

Code	Condition under which the code is used
2120.a	Obvious incoherence or abnormality or error in immune data
2120.b	Obvious incoherence or abnormality or error in CMI data
2120.c	Obvious incoherence or abnormality or error in Efficacy (sputum) data
2130.a	Subject bled for immuno but not planned to be bled
2130.c	Subject bled for CMI but not planned to be bled
2130.d	Subject bled for biomarker but not planned to be bled

5.2.2.2. 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
1060.x+	Unblinding of subjects
1070.x+	Subjects got vaccinated with the correct vaccine but containing a lower volume
1040.x	Subjects receive a vaccination forbidden by the protocol
2040.x+	Subjects receive a medication forbidden by the protocol

5.2.2.3. Visit-specific censored Data

Data from visit x will be censored 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
2090.x.y	Subjects did not comply with blood/sputum sample schedule at visit x
2100.a.x	Serological results not available for blood sample at visit x
2100.b.x	Bacteriological results not available for sputum sample at visit x
2130.x.y	Subject bled but not planned to be bled

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

The following important protocol deviations, which will not lead to elimination from analysis, will be reported by groups:

Manual randomization: In case of the randomization system is unavailable, the investigator has the option to call help desk and to perform a ‘manual’ randomization, which will be documented accordingly.

In case unexpected vaccinations at study start were granted due to regulatory recommendation, the subjects who had such vaccination could be mentioned.

Subjects for whom the spirometry could not be performed.

Subjects without chest X-ray available

Subjects of childbearing potential without pregnancy test for whom the pregnancy did not happen.

Possible violation from lab manual having no impact on sputum or blood results

Subject outside of AECOPD Visit windows

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Section 11 and will not be repeated below.

6.1. Demography

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

Demographic and baseline characteristics: age (in years), gender, ethnicity, smoking status at enrolment (i.e., screening visit) will be summarised by group using descriptive statistics.

Other variables GOLD grade at baseline, history of moderate and severe exacerbation in the last 12 months (<2 or ≥ 2, and total number), HRQOL baseline scores from CAT, SGRQ-C at enrolment visit (i.e., screening visit) will also be summarized as baseline characteristics.

- Frequency tables will be generated for categorical variable such as gender; geographical ancestry, age category, GOLD, smoking status and history of moderate and severe exacerbation;
- N, mean, median, standard deviation (SD) and min and max values will be provided for continuous data such as age, height, weight, body mass index (BMI), total number of exacerbation in previous 12 months and HRQOL baseline scores.

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

- Age in year (as continuous variable),
- Age category: 40-59 y, 60-80y
- Gender: Male, Female
- Race: (all reported in e-CRF)

- Ethnicity: Hispanic or Latino, Not Hispanic nor Latino
- Exacerbations in previous 12 months:
  - Total number
  - Mild
  - Moderate
  - Severe
- Exacerbations in previous 12 months category: <2, >=2
- Smoking status: yes, no
- Pack year (as continuous variable)
- GOLD grade category: 1 mild, 2 moderate, 3 severe, 4 very severe
- FE1/FVC category: >=70, <70
- CMI sub-cohort: yes, no
- Culture cohort: yes, no

The following variables will be included in vital sign summary and listing:

- Height (cm)
- Weight (kg)
- Body temperature (continuous variable)
- Body temperature category < 37.5°C, ≥ 37.5°C
- Hear rate
- Respiratory rate
- Systolic Blood Pressure,
- Diastolic Blood Pressure,
- Chest x-ray result: yes, no
  - Infiltrate presence (%): unilateral, bilateral
  - Pleural effusion (%): right chest, left chest, bilateral

Demographic and baseline characteristics will be tabulated for the Exposed Set (TVC) and mTVC, and no inferential analyses of are planned.

The distribution of subjects enrolled among the study sites and country will be tabulated as a whole and per group.

Number and percentages of subjects in each study cohorts (All enrolled, TVC, mTVC, FAS and PPS) will be summarized by 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 any cohort of analyses will be tabulated.

6.1.2. Additional considerations

Physical examination:

- As part of the baseline characteristics, variables collected during the physical examination such as height, weight, BMI, pulmonary function test baseline values (such as FEV_1/FVC, FEV_1 and FEV_1 % of predicted), body temperature, heart rate, respiratory rate, Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values will be summarized by the mean of descriptive statistics.

Body temperature will be also categorized as Fever YES (≥ 37.5°C (99.5°F)) or NO (< 37.5°C (99.5°F))

Haematology profile:

Haematology profile is defined at visit 1 only and the following parameters will be analysed form whole blood:

Whole blood	Leukocytes (White Blood Cells) Neutrophils Lymphocytes Eosinophils Basophils Monocytes Erythrocytes (Red Blood Cells) Hemoglobin Platelets

For each group and for each **haematology parameter** descriptive statistics such as: mean, median, standard deviation, minimum and maximum will be tabulated, together with the percentage of subjects having results below or above laboratory normal ranges.

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.
- Similarly the frequencies and percentage of subject who received influenza or pneumococcal vaccination in the previous 12 months before enrollment will be reported overall and by vaccine group

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccinations will be summarized overall and by vaccine group. Data will be tabulated for the Exposed Set.

6.2.2. Additional considerations

None.

6.3. Efficacy/Effectiveness

Efficacy of the vaccine will be evaluated as both primary and secondary endpoints.

In the primary endpoint analysis, the 'clinical' vaccine efficacy is defined as reduction in 12 months rate of moderate and severe AECOPD (any cause) from one month after complete vaccine exposure.

In secondary endpoints a broader definition for efficacy is being investigated and the following rates are considered:

- Reduction in 3, 6, and 9 months rate of moderate and severe of AECOPD (any cause) starting from one month after complete vaccine exposure.
- Reduction in yearly rate of any grading of AECOPD (any cause) starting from one month after complete vaccine.
- Reduction in severity of AECOPD (any cause) starting from one month after complete vaccine.
- Reduction in yearly rate of moderate and severe of AECOPD associated with NTHi or Mcat, starting from one month after complete vaccine.
- Reduction in yearly rate of any grading of AECOPD associated with NTHi or Mcat, starting from one month after complete vaccine.
- Reduction in 3, 6, and 9 months rate of moderate and severe AECOPD associated with NTHi or Mcat starting from one month after complete vaccine exposure.
- Reduction in severity of AECOPD associated with NTHi or Mcat starting from one month after complete vaccine.

6.3.1. Analysis of efficacy planned in the protocol

The efficacy analysis will be performed on the mTVC and repeated on the TVC and on the FAS. The primary efficacy analysis will also be repeated on the PPS if the percentage of vaccinated subjects excluded from the PPS for efficacy is more than 5%.

In the TVC cohort, if a subject receives only one dose the efficacy endpoint is defined as the number of (moderate or severe) AECOPD (any cause), occurring within a period starting from Day 90 and lasting for 1 year (i.e., until study conclusion).

Vaccine efficacy (VE) is expected to start at one month post-Dose 2 (Day 90), so the study period is divided in to two: from enrolment (Day 1 - day of first injection) up to one month post Dose 2 (Day 90) and from one month post Dose 2 (Day 90) until study end (Day 451).

Evaluation of VE and incidence rate of AECOPD in both study groups, together with CIs will be computed for each study periods.

6.3.1.1. Efficacy – Clinical Endpoints

6.3.1.1.1. Primary Analyses

The primary analysis method of the vaccine VE will consider the exact inference on the risk ratio (R_{vacc} / R_{con}) based the total number of moderate and severe AECOPD observed in one year time of follow up.

VE is defined as: $VE = 1 - R_{vacc} / R_{con}$

being

- R_{vacc} = average yearly incidence rate of AECOPD events per subject in the group 10-10-3-AS.
- R_{con} = average yearly incidence rate of AECOPD events per subject in the placebo group.

Inferential statistic

Incidence rates and VE with 87% and 95% CIs will be tabulated for primary efficacy endpoint. P-value (to test H_0 = [VE=0]) will be tabulated for the primary endpoint.

The efficacy of vaccine in preventing moderate and severe AECOPD will be demonstrated if the lower limit of the two-sided 87% CI of VE is above 0.

The primary outcome will be analysed using the Negative Binomial regression model with number of AECOPD as dependent variable; treatment (vaccine or placebo), age group (40 - 59 yrs or 60 - 80 yrs), GOLD grade (2, 3 or 4) and history of moderate and severe exacerbations (<2 or ≥ 2) and country as independent variables, with logarithm as link function, and the logarithm of time for follow-up (in years) as an offset variable.

The following SAS code will be applied for primary analysis:

```
PROC GENMOD data=<dataset>;
 CLASS trt age gold hexac country;
 MODEL nb_exac = trt age gold hexac country
      / dist=NegBin LINK=log OFFSET=logfu alpha=0.13;
RUN;
```

Where
trt= treatment arm;
age= Age Group
nb_exac=number of exacerbation
gold= GOLD grade at enrolment;
hexac= History of moderate/severe exacerbation;
country=Subject Country
fu= follow up time in year;
logfu= log(fu);

Point estimate and CIs of the incidence rate for each arm, will be computed using a simple Negative Binomial model, without covariates and thus the following SAS code will be applied:

```
PROC GENMOD data=<dataset>;
BY trt;
MODEL nb_exac =       / dist =NegBin LINK=LOG OFFSET=LOGFU alpha=0.05;
ODS OUTPUT ParameterEstimates=out_parm NObs=Nobs;
RUN;

DATA parm_est(keep= val rate rate_LL rate_UL);
 SET out_parm(WHERE=(Parameter='Intercept'));
 format rate rate_LL rate_UL 8.2;
      val= "Yearly Rate from Negative Binomial";
      rate=EXP(Estimate);
      rate_LL=EXP(LowerWaldCL);
      rate_UL=EXP(UpperWaldCL);
 RUN;
```

Note: If the model does not converge, the Poisson distribution will be used instead of the Negative Binomial.

The number of AECOPD occurring from enrolment up to 1 month post-Dose 2 will be used as 'baseline' value. No difference between vaccine and placebo is expected in this period.

Descriptive statistics

For each treatment group, the total number of subjects, total number of AECOPD, total exposure time (in days), and incidence exacerbation rate (per year and per each sub period considered) together with the frequency of number of AECOPD will be tabulated.

The following statistics will be reported for exacerbation rate in the two treatment groups: N, mean, SD, median, Q1, Q3, min and max.

Sensitivity analysis

Primary analysis will be presented in three study populations: mTVC, TVC, FAS and PPS. In addition, a sensitivity analysis will be carried out using permutation test.

Permutation test procedure

The null distribution of Z to test H0 (i.e., β=0 or VE=0) will be obtained by re-randomizing treatment assignment according to the original minimization algorithm (Section 11.3) while keeping outcomes and covariates as observed. The procedure to follow is described below:

1. Fit the regression model to obtain the test statistic Z to test H_0 (i.e., β=0 or VE=0)
2. Estimate the null distribution for the test statistic Z with N (=10000) replicates of the two following steps :
   a. Re-randomize treatment assignment using minimization.
   b. Re-fit the regression model to re-derive the test *Z*
3. Derive the empirical p-value for the test statistic Z from the null distribution based on the permutation distribution

$p_{(permutation\ test)}=(M)/(N)$

Where M denotes the number of replicates for which the test statistic *Z* obtained in the permutation procedure is equal to or greater than (in absolute value) the observed value of Z obtained in 1, and N denotes the number of replicates (i.e., 10000).

6.3.1.1.2. Secondary Analyses

Incidence rate of AECOPD

The following incidence rates of AECOPD (any type) occurring from enrolment up to 1 month post-Dose 2 will be computed together with 95% CIs, and incidence rates together with VE in the prevention of AECOPD (any type) will be computed over a period starting 1 month post-Dose 2 and lasting for 1 year, with 95% CIs:

- Any severity of AECOPD.
- AECOPD, by event severity.

Time to first AECOPD event

The time to first AECOPD events following complete schedule vaccination (i.e., 1 months post-Dose 2) will be analysed using Cox's proportional hazard regression model which include, with treatment, GOLD grade at enrolment (2, 3 or 4) and history of exacerbations (<2 or ≥ 2) as factors. Wald test and CIs will be produced.

The time to first event will be computed for the following:

- Time to first moderate and severe AECOPD
- Time to first any severity AECOPD.
- Time to first AECOPD, by event severity.

Hazard rate and CI will be derived using the following SAS code:

```
PROC PHREG data=<dataset>;
CLASS trt age gold hexac;
MODEL survtime*status(0)=trt age gold hexac / TIES=EXACT RISKLIMITS;
RUN;
```

In addition the survival curves for each vaccine group will be calculated non-parametrically, and presented graphically using the Kaplan-Meier (i.e., Product-Limit) method, using the following code:

```
PROC LIFETEST data=<dataset> method =KM plot=(survival(atrisk) logsurv);
TIME survtime*Status(0);
STRATA trt;
RUN;
```

survtime represents variable containing AECOPD times.
status represents censoring variable (0=censored, 1=event).

Duration of AECOPD event

The length of each AECOPDs will be tabulated and presented via descriptive statistics (mean, SD, median, Q1, Q3, minimum and maximum), for each treatment and for the two periods (before 1 month post-Dose 2 and after 1 month post- Dose 2).
Tables will be produces considering the following:

- Duration of moderate and severe AECOPDs.
- Duration of AECOPDs of any severity.
- Duration of AECOPDs, by severity.

Stratification and additional analysis

Incidence rates of AECOPD and VE, together with 95% CIs, will be computed for all study period (starting from day 1 until study termination) and at 4, 7, 10 and 13 months post-Dose 2, using the same model as for the primary analysis.

Similarly for the time-to-event and duration of AECOPD data will be also presented for the entire study period starting from Day 1 up to study termination.

In addition descriptive statistics for the incidence rates will be presented by patient severity (GOLD grade: 2, 3, or 4), by Country (USA, Canada, France, Spain, Belgium, UK, Germany and Italy), by history of exacerbations (< 2 or ≥ 2) and by age group (40 - 59 yrs or 60 - 80 yrs).

6.3.1.2. Efficacy – Bacteriological Endpoint (PCR)

An AECOPD will be considered 'associated' to NTHi and/or Mcat if the sputum sample, collected during AECOPD visit, will reveal the presence of those bacteria.

We can assume that more than 99% of *H. influenzae* isolates in sputum (derived from lung) are non-typeable (NTHi) (Wilkinson, 2017) and thus the presence of Hi bacteria in sputum during exacerbation will be used to determine AECOPD associated to NTHi.

In case of no sputum sample at such visit, or no bacteriological presence (i.e., Hi or Mcat) the event will not be counted.

Bacteriological vaccine efficacy (VE_{bact}) is defined as reduction in number of NTHi and/or Mcat associated AECOPD in vaccinated subjects compared to placebo subjects:

$VE_{bact} = 1 - R_{vacc} / R_{con}$

where

- R_{vacc} = average yearly incidence rate of AECOPD events associated to NTHi and/or Mcat per subject in the group 10-10-3-AS.
- R_{con} = average yearly incidence rate of AECOPD events associated to NTHi and/or Mca per subject in the placebo group.

VE_{bact} in prevention of NTHi and/or Mcat associated AECOPD will be evaluated via PCR method in all subjects. The statistical analysis will be performed in a modified TVC (mTVC) population as first line and repeated in the PPS cohort if more than 5% of subjects are excluded.

The mTVC is defined as all subjects in the TVC (i.e. ES) who provide sputum sample results.

The following incidence rate together and VE_{bact} over a period starting 1 month post-Dose 2 and lasting for 1 year and its 95% CIs will be computed:

- NTHi and/or Mcat-associated moderate and severe AECOPD.
- NTHi and/or Mcat-associated all-severity AECOPD.
- NTHi and/or Mcat-associated AECOPD, by severity.
- The time until first moderate and severe NTHI and/or Mcat- associated AECOPD.
- The time until first NTHI and/or Mcat- associated AECOPD (any severity).
- The time until first NTHI and/or Mcat- associated AECOPD by severity.

In addition incidence rates of AECOPD associated to NTHi and/or Mcat, and VE_{bact}, together with 95% CIs will be evaluated for all study period starting from Day 1 until study completion and counting the AECOPD at 4, 7, 10 and 13 months post-Dose 2.

Inferential statistic

Number and proportion of sputum samples (obtained at each scheduled visits and at each AECOPD visits) positive for bacterial pathogens (Hi and/or Mcat) will be computed together with exact 95% CIs by group and overall. The exact CIs will be estimated assuming independence of bacterial results across sputum samples.

The bacteriological vaccine efficacy outcome will be evaluated using same model as for clinical efficacy with the following SAS code:

```
PROC GENMOD data=<dataset>;
 CLASS trt age gold hexac country;
 MODEL nb__bact_exac = trt age gold hexac country
      / dist=NegBin LINK=log OFFSET=logfu;
RUN;
```

Where

nb_bact_exac are AECOPD associated to NTHi and/or Mcat by PCR method

As for the primary endpoint the number of bacterial associated AECOPD occurring from enrolment up to 1 month post-Dose 2 will be used as 'baseline' value. No difference between vaccine and placebo is expected in this period.

Descriptive statistics

For each treatment group, the total number of subjects, total number of AECOPD associated to NTHi and/or Mcat, total exposure time (in days), incidence of bacteriological associated exacerbation rate (per year and per each sub period considered) and the frequency of number of AECOPD will be tabulated.

The following statistics will be reported for AECOPD associated to NTHi and /or Mcat: N, mean, SD, median, Q1, Q3, min and max.

6.3.1.3. Efficacy – Bacteriological Endpoint (culture)

Same set of analyses, as in the PCR efficacy bacteriological endpoint, will be performed in the subset of subjects for whom the culture sputum (collected at AECOPD visits) is performed

Approximately 50% of the subjects will be allocated to sputum culture analysis (depending on which site the subject belongs as not all sites are qualified and selected for culture analysis).

The selection of sites that will perform the sputum culture is based on site characteristics (i.e., presence of qualified laboratory) and only subjects enrolled in these sites will be considered for this analysis.

The analysis will be performed in the culture-subset of the modified TVC (mTVC) population. The mTVC is defined as all subjects in TVC (ES) and in the subset for culture sample who provide valid culture sputum sample results.

6.3.2. Additional considerations

The number of AECOPD occurring during the 1 year follow-up period starting 1 month post-Dose 2 will be used to describe vaccine efficacy (VE). Exacerbation rate reported during this period will be calculated for each subject.

Only for the purpose of reporting summary statistics, the number of exacerbations during the 1-year follow-up will be imputed for subjects withdrawing from the study to provide an estimate of the number of exacerbations over the follow-up period. This calculation will only be performed for the descriptive statistics for the rate of exacerbations during 1 year follow up period since the modelling of exacerbations takes into account the number of exacerbations and the time of follow-up for each subject [see Section 11].

Incidence rate of AECOPD will be also computed in sub period starting from 1 month post-Dose 1 up to 3, 6 and 9 months, and stating from Day 1 up to entire study duration (i.e., 1 year and 3 months).

Control of type I error

Inferential analyses for efficacy are planned to be performed at alpha level of 0.13 (two sided). No alpha adjustment for multiple testing in the secondary endpoints will be performed, nevertheless efficacy analysis, both primary and secondary endpoints will be also complemented with the 95% CI.

6.4. Immunogenicity and Cell-mediated Immunity (CMI)

6.4.1. Analysis of immunogenicity planned in the protocol

As first line, the immunogenicity analysis will be based on the PPS (ATP). If the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is more than 10%, a second line immunogenicity analysis will be performed on the TVC.

Within group assessment

For each group (i.e., vaccine and placebo), at each timepoint during which blood samples are collected for humoral immune response (i.e., Day 1, Day 31, Day 61, Day 91, Day 271 and at Day 451), and for each vaccine strain (i.e., PD, PE, PilA and UspA2), the following will be computed:

- Seropositivity rate and the associated exact 95% CI
- GMCs and the associated 95% CI

Seropositivity rate is defined a percentage (proportion) of seropositive subjects. Seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value, as specified in Table 2

Descriptive statistics

The $\log_{10}$ ELISA concentration and fold increase over pre-exposure (i.e., Day 1) will be tabulated via descriptive statistics such as N, mean, SD, median, min, max and 95% CI for each group, study visit (where immune blood draw is performed) and vaccine strain.

Similarly the proportion of seropositivity subjects will be tabulated together with N, number of seropositive subjects and percentage for each group, study visit and vaccine strain.

In addition the distribution of antibody concentrations for each strain will be displayed using Reverse Cumulative Distribution Curves (RCDF).

The percentages of subjects with positive (see Table 2) ELISA values (on log10 scale) will be plotted via RCDF, having the individual concentration on the X-axis and the percentage of subject with equal to or greater than the value on the Y-axis by strain and visit.

Between groups assessment

The between groups immunogenicity analysis will be carried out with an alpha =0.05, however these are descriptive comparisons with the aim to characterize the difference between groups and should be interpreted with caution considering that there will be no alpha adjustment for multiplicity.

GMCs and GMCs ratio

The difference between vaccine and placebo will be evaluated in terms of GMCs ratio (Vaccine/Placebo) and it will be tabulated for each time together with the 95% CIs of the GMC ratio between groups by using an ANCOVA model on the logarithm base10 transformation of the concentrations. This model will include the group (vaccine or control), age category (40 - 59 years or 60 - 80 years), GOLD grade (GOLD 2, GOLD 3 or GOLD 4) and country as fixed effects and pre-Dose 1 concentration (as covariate).

For each vaccine group and time point (Visit), adjusted GMCs, GMC ratios and their 95% CIs will be obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% CIs of the log10-transformed concentrations. These will be obtained from an ANCOVA with vaccine group, age category, GOLD grade, country and pre-Dose 1 concentrations, as implemented in the following SAS code:

```
PROC GLM data=<dataset>;
BY visit;
class trt age gold country;
MODEL log(titer) = trt age gold country log(prettier);
LSMEAN trt / CL PDIFF ALPHA=0.05;
RUN;
```

Seropositivity: proportion and difference between proportions.

The vaccine group difference will be also evaluated in terms seropositivity proportion difference calculated using a binomial distribution. For constructing the 2-sided 95% CIs for the difference between groups the usual normal approximation is not considered to be appropriate because these proportions could be close to 1. Therefore, the associated confidence interval for the differences in percentage will be constructed using the MN method (Miettinen, 1985). In analyzing differences in proportions, the MN method assumes normality of the test statistic (or a chi-square distribution for the squared version) under the null hypothesis and the difference with the usual method is in the variance estimation. This method is implemented in SAS with the following code:

```
PROC FREQ data= <dataset>;
TABLES trt*count / RISKDIFF(CL=MN) ALPHA=0.05 ;
WEIGHT frequency / zero;
RUN;
```

Table 2 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit*	Cut-off*	Laboratory
SERUM	anti-PD antibody	ELISA	In house	EU/ml	153	GSK Biologicals** or GSK designated laboratory
	anti-PE antibody				25	
	anti-PilA antibody				16	
	anti-UspA2 IgG antibody				38	

EU/ml = ELISA unit per millilitre

* 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.

6.4.2. Analysis of CMI planned in the protocol

CMI analysis will be descriptive only and it will be performed in a subset of approximately 120 subjects for whom the CMI blood samples are collected (*see protocol* section 5.1 Number of subjects).

CMI analysis will be based on the PPS (ATP). If more than 10% will be excluded from the PPS for CMI, a second line CMI analysis will be performed on the CMI subset of the TVC (i.e., All subjects with at least 1 documented study vaccine administration and for whom CMI data are available).

NTHi and Mcat- specific CMI responses as measured by flow cytometry ICS

Descriptive statistics

For each vaccine strain (PD, PE, PilA and UspA2) the frequency of specific $CD4^+$T-cells producing two or more markers (see Table 3) will be summarised by means of descriptive statistics (mean, SD, minimum, Q1, median, Q3, and maximum) for each group, and at

each time point during which blood samples are collected for CMI subset (Day 1, Day 91, Day 271 and Day 451).

The frequency of CD4+ T-cells producing two or more markers upon in vitro stimulation with the antigen (induction condition) is presented per million of CD4+ T cells for the analysis and in percentage for the graphical representation (via BOX-plot).

The Geometric Mean (GM) frequency at each CMI timepoint (Day 1, Day 91, Day 271 and Day 451) and for each stimulation (vaccine strain) will be also computed by taking the anti-log of the mean of the log frequency transformations.

Table 3 Intracellular cytokines staining (Markers)

Method	Unit	Cytokine	Cytokine Label
Flow cytometry ICS	Number of specific CD4+T-cells /10^6	CD40L	CD40 Ligand
		IL-2	interleukin 2
		IL-13	interleukin 13
		IL-17	interleukin 17
		IFN-γ	interferon gamma
		TNF-α	tumour necrosis factor alpha

T helper profile

T helper profile of the specific CD4+ and CD8+ T cells response will be evaluated with the frequencies of strain (stimulation) specific $CD4^+$/ $CD8^+$ T-cells expressing each cytokine and will be summarised by means of descriptive statistics (mean, SD, minimum, Q1, median, Q3, and maximum) for each group and at time point: Day 1, Day 91, Day 271 and Day 451 and via BOX plot.

6.4.3. Additional considerations

Humoral immune response

Missing immunogenicity data are considered missing completed at random (MCAR) and therefore will not contain information that impact the results of the analysis (i.e., not informative). Imputation methods will therefore not be used.

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.

Cell-mediated immune response

The frequency of CD4+ T-cells expressing a marker (see Table 3) is presented per million of cells for the analysis and per hundred cells for the graphical representation.

The frequency of antigen-specific CD4+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ T-cells producing at least 2 cytokines, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of

CD4+ T-cells producing at least 2 cytokines upon in vitro stimulation in medium only (background condition).

$$\boldsymbol{Freq}^{2+}_{\boldsymbol{Induction}} = \frac{\boldsymbol{n}^{2+}_{\boldsymbol{Induction}} - \boldsymbol{n}^{2+}_{\boldsymbol{background}}}{\mathbf{1000000}} \quad \boldsymbol{Log_e}\left(\boldsymbol{Freq}^{2+}_{\boldsymbol{Induction}}\right) = \boldsymbol{Log_e}\left(\frac{\boldsymbol{n}^{2+}_{\boldsymbol{Induction}} - \boldsymbol{n}^{2+}_{\boldsymbol{background}}}{\mathbf{1000000}}\right)$$

$n^{2+}_{Induction}$ = Number of antigen-specific CD4+T-cells expressing two or more cytokines.

Each data will be obtained by subtracting the summary of the background value to each summary value. Values less than or equal to zero will be set to 1 for the purpose of geometric mean calculation and graphical representation.

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The safety analysis will be based on the ES (also called TVC).

All analyses will be based on the ‘as treated’ analysis set.

Safety analysis will be descriptive, no inference and formal statistical comparison is planned for the safety data.

Safety reporting period differs depending on safety endpoints. Table 4 shows the overview of the safety reporting

Table 4 Reporting periods for collecting safety information

Event	Screening	Visit 1 Dose 1	6 d post Dose 1	29 d post Dose 1	Visit 3 Dose 2	6 d post Dose 2	29 d post Dose 2	6 m post Dose 2	Study Concl
Timepoint	Visit*	Day 1	Day 7	Day 30	Day 61	Day 67	Day 90	Day 241	Day 451
Solicited local and general AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
SAEs									
SAEs related to study participation or concurrent GSK medication/ vaccine									
Pregnancies									
pIMDs									
Intercurrent medical conditions									

* i.e. consent obtained.
The double-bordered lines indicate timings of vaccination.
AE = adverse event; SAE = Severe adverse event; GSK = GlaxoSmithKline; pIMD = potential immune mediated diseases

6.5.1.1 Solicited Local and General Adverse Events:

The following local AE will be solicited for 7 days after each vaccination:

Table 5 Solicited local adverse events:

Local AE	Grading	Collection period
Pain at injection site	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
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 Day 61-Day 67
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 diameter0	Day 1-Day 7 Day 61-Day 67

The percentage of subjects with at least one local solicited AE reported in diary card within 7 days after each dose (Day 1-Day 7) will be tabulated together with the exact 95% CI. Similarly the percentage of doses followed by at least one local solicited AE will be tabulated together with the exact 95% CIs within each group.

The same tabulation will be done for grade 3 solicited local AEs.

The following general AE will be solicited for 7 days after each vaccination:

Table 6 Solicited general adverse events:

General AE	Grading	Collection period
Headache	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Fatigue	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Myalgia	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Chills	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
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 Day 61-Day 67

The percentage of subjects with at least one general solicited AE reported in diary card within 7 days after each dose (Day 1-Day 7) will be tabulated together with the exact 95% CI. Similarly the percentage of doses followed by at least one general solicited AE will be tabulated together with the exact 95% CIs within each group.

The exact 95% CIs will be calculated assuming independence between doses

The same tabulation will be done for grade 3 solicited general AEs.

The percentage of subjects reporting each individual local and general solicited AEs during the solicited follow-up period (i.e., day of vaccination and six subsequent days after each vaccination) by grading will be tabulated with exact 95% CI after each dose and overall by group. The percentage of doses followed by each individual solicited local and general AE will be tabulated overall by group with exact 95% CIs [*Clopper, 1934]*

The exact 95% CIs will be calculated assuming independence between doses.

For fever (irrespective of route of measurement), additional analyses will be performed 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

6.5.1.2 Unsolicited Adverse Events:

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 e-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 (SOC) and preferred term within SOC. 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.

The percentage of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) during a 30-day follow-up period after each dose (Day 1 –Day 30) will be tabulated with exact 95% CI for each group. The same tabulation will be performed by severity, and for unsolicited AEs with a relationship to vaccination.

SAEs, death, pIMDs and AE leading to withdrawal reported during the entire study will be tabulated (from Day 1 until study termination) and listed.

In addition, SAEs related to study participation or concurrent GSK medication/vaccine reported from inform consent signed until entire study duration will be also listed.

This study foreseen two injections (i.e., two vaccinations) for each subject, and thus unsolicited AEs summary tables will be presented overall and by period of onset and will include frequency distributions of the different adverse events:

Number and percentage of subjects with the following AEs will be computed:

<u>Onset between day 1 and Day 30 after each vaccination:</u>

- Any AE after each vaccination (overall)
- Any AE after each vaccination, by vaccination
- By severity AE after each vaccination (overall)
- By AE severity after each vaccination, by vaccination
- Possibly or probably related unsolicited AEs after each vaccination (overall)
- Possibly or probably related unsolicited AEs after each vaccination by vaccination
- Possibly or probably related unsolicited AEs by severe after each vaccination (overall)
- Possibly or probably related unsolicited AEs by severe after each vaccination by vaccination
- Any medically attended unsolicited AE (overall).
- Any medically attended unsolicited AE, by vaccination

<u>Onset between day 1 and Day 450 (study termination):</u>

- Any serious adverse events (SAE) (overall).
- Any serious adverse events (SAE) by vaccination.
- Possibly or probably related SAE (overall).
- Any AE leading to death (overall).
- Any unsolicited AE leading to premature withdrawal from study (overall).
- Any potential immune mediated diseases (overall)

- Any potential immune mediated diseases by vaccination
- Any AE leading to hospitalization (overall).

Onset between Screening and Day 450 (study termination):

- Any SAE related to study participation or concurrent GSK medication or vaccine (overall).

6.5.2. Additional considerations

For solicited symptoms, missing or unevaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC (also called ES) will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

Solicited adverse events continuing beyond day 7 will be followed until resolution (up to Day 30). Solicited AEs which will start after the day 1- day 7 after vaccination will be reported as unsolicited AE and coded by MedDRA as per Table 7.

For the unsolicited symptoms and concomitant medications/ products/ vaccinations, all vaccinated subjects will be considered and subjects who miss reporting symptoms/concomitant medications/ products/ vaccinations will be treated as subjects without unsolicited symptoms or concomitant medications/ products/ vaccinations, respectively.

6.5.2.1. Exclusion of implausible solicited Adverse Event

Some local and general 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 7:

Table 7 Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Redness	≥ 900 mm < 0 mm
Swelling	≥ 500 mm < 0 mm

6.5.2.2. 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:

Table 8 MedDRA coding for solicited AE

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

The following results will be tabulated:

The percentage of subjects with at least one **local type AE** (solicited and unsolicited), with at least **one general** adverse event (solicited and unsolicited) and with **any AE** during the solicited follow-up period, i.e., the day of vaccination and six subsequent days after each vaccination will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be done for grade 3 AEs.

The percentage of doses followed by at least one **local AE** (solicited and unsolicited), by at least one **general AE** (solicited and unsolicited) and by **any type AE** will be tabulated, overall vaccination course, with exact 95% CI. The same tabulation will be done for grade 3 AEs.

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events is requested by System Organ Class and preferred terms and according to occurrence of each event. For this purpose the following additional analysis will be produced:

- The number of occurrence of the 5% most frequent non-serious unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination.
- The number of occurrence of SAE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination.

6.5.2.3. Pregnancies:

In case of any pregnancy from visit 1 (first vaccination) up to entire study duration, pregnancy reports and outcomes will be reported.

6.5.2.4. Clinical Safety Laboratory Investigations

Haematology profile, including differential cell counts is performed only at visit 1, before vaccination, and it will be summarized as baseline characteristics (see section 6.1.2) via descriptive statics. For each parameters: N, mean, median, SD, min and max will be computed and the frequencies of subjects with values above or higher normal ranges by treatment group.

6.5.2.5. Concomitant Medication

This analysis will consider all medications taken (and reported) for different purpose then COPD or AECOPD. The analysis of medications to treat COPD or AECOPD (standard of care and not standard of care) is described in section 6.6.2.

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects starting/reporting concomitant medications within the 7-day follow-up period (day 1 – day 7), during the 30-day follow-up period (day 1 – day 30) post-vaccination and during the entire study period will be tabulated by vaccine group for each study dose and across doses.

6.6. Other Analysis

6.6.1. Microbiological assessment

6.6.1.1. Sputum sample collection and quality

Sputum sample collection

Patient sputum sample will be collected (as stable visit) at Day 1 (before vaccination) and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD driven visit, where AECOPD is confirmed.

Within each vaccine group the percentage of patients at each study visit (stable visit) and AECOPD confirmed visit will be computed overall and by the method (i.e., spontaneous at study visit or spontaneous at patient's home, induced using 0.9% saline or induced using 3% saline).

The proportion of sputum samples obtained at each stable or AECOPD visit and positive for specific bacterial pathogens by bacteriological culture and PCR will be computed, by vaccine group.

Sputum sample quality

The quality of sputum is assessed via squamous cells count, neutrophils cells count and bacteria direct smear. These will be summarized at any sputum visit (stable) and at any AECOPD confirmed visit, via frequencies tables (i.e., frequencies of sputum

samples per quality scores [see section 11.2.7 in Section 11] within each vaccine e group)

If more than 10% of sputum samples have bad quality the analyses of bacteriological efficacy endpoint and bacteriological load (via PCR and culture) will be repeated in the subset of sputum samples with good and moderate quality.

6.6.1.2. Sputum bacterial/viral results via qPCR

Occurrence and load of Hi and/or Mcat

For each vaccine group the following analysis will be presented for sputum sample analysed via PCR:

- Overall proportion of sputum samples positive for Hi and Mcat with associated 95% CIs before vaccination (Day 1) and at any stable visit (Day 91, Day 181, Day 271, Day 361, Day 451) Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit
- Proportion of patients with sputum samples positive for Hi and Mcat with associated 95% confidence intervals (CIs), at each stable visit and at each AECOPD visit confirming acute exacerbation
- Summary statistics (N, mean, SD, median, minimum and maximum) and 95% CIs for the Hi and Mcat load will be displayed at each stable visit and at each AECOPD visit.

For the overall proportion, estimate and confidence intervals will be computed using a Generalized Estimating Equations (GEE) model assuming a binomial distribution for the response variable with logit as link function and a compound symmetry correlation matrix (exchangeable structure) to account for the within-patient correlations (Liang,. 1986) and the following SAS code will be apply for stable visits, AECOPD visits separately and for Hi and Mcat bacteria:

```
PROC GENMOD data=<dataset> descending;
CLASS pid trt;
BY bacteria;
MODEL sp_positive = trt / dist = bin LINK = logit lrci ;
REPEATED subject=pid/ type=exch PRINTMLE;
ODS OUTPUT ParameterEstimates=out_parm ClassLevels=Class;
RUN;

DATA result;
 SET out_parm(where=(parameter='Intercept') drop=ChiSq ProbChiSq DF);
 format percent LL UL percent8.1;
      Percent=exp(estimate)/(1+exp(estimate));
      LL=exp(LowerLRCL)/(1+exp(LowerLRCL));
      UL=exp(UpperLRCL)/(1+exp(UpperLRCL));
      unit=_N_;
RUN;
```

where:
pid: patient id
trt= treatment arm;
sp_positive=sputum sample positive to bacteria (Hi or Mcat)

Other bacteriological pathogens

In addition to proportion of sputum positive to Hi (*Haemophilus influenza)* and Mcat (*Moraxella catarrhalis)* also the proportion of sputum samples obtained from PCR at pre-vaccination (Day 1), at Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit that are positive for specific bacteria (such as *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and *Streptococcus pyogenes* [*S. pyogenes*]) and virus (such as *respiratory* syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) will be presented together with the 95% CIs.

6.6.1.3. Sputum bacterial/viral results via culture

In the subset of subjects from whom the sputum will be analysed also by culture, the proportion of subjects with sputum sample positive and the number and proportion of sputum sample positive to Hi (with or without the *H. influenzae* confirmation by PCR of the collected bacterial isolates) and Mcat by culture will be displayed at each stable visit and at each AECOPD visit together with the 95% CIs, within each treatment group, using the same method as for PCR.

Frequencies of semi-quantitative bacteriological load (few scattered, +, ++, +++), for each vaccine group will be tabulated.

Other bacteriological pathogens

In addition to proportion of sputum positive to Hi (*H. influenza)* and Mcat (*M. catarrhalis)*, also the proportion of sputum samples at pre-vaccination (Day 1), at Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit that are positive to *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and other bacteria identified via culture, will be presented together with the 95% CIs.

6.6.2. Health related quality of life (QOL)

The following analysis are exploratory and a p-value <0.1 will be considered statistically significant, however 2-sided 95% CIs will be computed to show precision of estimation. All comparisons should be interpreted with caution considering that there will be no adjustment for multiplicity.

For each of the following questionnaire missing items will not be imputed and subjects with partial data will be excluded.

EXACT-PRO daily score

The EXAcerbations of Chronic pulmonary disease Tool (EXACT) constitutes of 14 items which are patient-reported outcome (PRO) via daily diary.

All EXACT-pro scores will be divided in to the following periods:

- Screening: scores collected between screening and Visit 1 (Baseline)
- Treatment: scores collected between Visit 1 and Visit 4 (i.e., 1 month post-Dose 2)
- Exacerbation: scores collected during the start date of an exacerbation until resolution.
- Follow –up: scores collected between Visit 4 (one month post-Dose 2) until study completion (one year after - Visit 8).
- Follow-up will be also divided by 3 months sub period:
  - from Visit 4 to Visit 5 (Day 91 to Day 180)
  - from Visit 5 to Visit 6 (Day 181 to Day 270)
  - from Visit 6 to Visit 7 (Day 271 to Day 360)
  - from Visit 7 to Visit 8 (Day 361 to Day 450)

Descriptive statistics

For each subject the average score across all days, within each period is computed. The mean score will be reported as descriptive statistics within each group (i.e., vaccine and placebo). N, mean, SD, median, min and max, on the **EXACT-PRO** average scores will be tabulated during all (stable) periods and during exacerbations.

Between groups comparison

At each period and sub period the two groups will be compared using an ANCOVA model, with the baseline value (i.e., score at screening) as covariate and treatment as fixed factor.

Note: EXACT-PRO baseline score at screening will be computed as the average within-patient score collected between screening Visit and Visit 1. If fewer than 4 days scores are available, the EXACT-PRO baseline score cannot be calculated and it will results as missing.

COPD Assessment Test (CAT)

COPD Assessment test (CAT) is a patient-completed questionnaire assessing globally the impact of COPD (cough, sputum, dyspnoea, chest tightness) on health status. It constitutes of 8 items each scoring from 1 to 5. The Total score is given by the sum of the single item scores and it ranges from 0 to 40. Higher scores denote a more severe impact of COPD on patient's life.

CAT questionnaire will be provided to all enrolled patients at Screening, Day 271 and Day 451 (end of study), and at each AECOPD visit.

Descriptive statistics

Descriptive statistics (N, mean, SD, median, Q1 and Q3, min and max) on the CAT total score (obtained as sum of the scores of 8 single items) will be reported by scheduled visits (stable visits), by AECOPD visit and by each treatment group.

Data will be also represented via line-chart for the total score at each time points (screening, Day 271, Day 415 and any AECOPD visit) together with the 95% confidence interval around the mean of the total score.

Within group change

For each group and at each time point (Screening, Day 271 and Day 421), the mean of total score together with SD will be reported and a pair t-test will be performed to compare screening scores with scores at Day 271 and at Day 421.

Between groups comparison

Differences between groups will be analysed in terms of difference in mean for each time points (Day 271 and Day 421) by one-way ANOVA model on the total scores, with vaccine group as factor.

CAT Score at AECOPD Visit

N, mean, SD, median, Q1 and Q3, min and max CAT score during AECOPD visit will be displayed according to the number and severity of AECOPD event.

St. George's Respiratory Questionnaire assessment (SGRQ-C)

The St. George's Respiratory Questionnaire (SGRQ) is composed of 76 items that are weighted to produce three component scores: Symptoms: measuring distress caused by respiratory symptoms, Activity: measuring the effect of difficulties in mobility and physical activity, and Impact: quantifying the psychosocial impact of the disease.

A "Total" score is also computed as sum from all component items score, thus providing a global estimation of the patients respiratory health. Each of these scores ranges from 0 to 100, a score of 100 indicating maximum disability (*Jones, 1991*)

SGRQ-C will be provided to all enrolled patients at Screening, Day 271 and Day 451 (end of study), and at each exacerbation visit.

Descriptive statistics

Descriptive statistics (N, mean, SD, median, Q1, Q3, min and max) on the SGRQ-C (total score and symptoms, activity and impacts component scores) will be reported by scheduled visits (stable visits), at each AECOPD visit and by each treatment group.

Mean score for each component (symptoms, activity and impacts) and mean total scores will be also represented via line-chart at each time points (screening, Day 271, Day 415 and any AECOPD visit) together with the 95% confidence interval around the mean.

Within group change

For each group and at each time point (Screening, Day 271 and Day 421), the mean of each component score and the mean of total score together with SD will be reported and a pair t-test will be performed to compare screening scores with scores at Day 271 and at Day 421.

Between groups comparison

For all components and for the total scores, differences between groups will be analysed in terms of difference in mean for each time points (Day 271 and Day 421) by one-way ANOVA model on the total scores, with vaccine group as factor.

SGRQ-C at AECOPD Visit

N, mean, SD, median, min and max, of each component scores and of total score during AECOPD visit will be displayed according to the number and severity of AECOPD event.

Use of medication to treat (AE)COPD and Healthcare utilization (HCU)

Frequency table on the number and type of healthcare utilisation (Physician's office, Visit to Urgent Care, Visit to Emergency Department, Hospitalization) during entire study period will be presented overall and by vaccine group.

Same frequency table will be also presented for two sub-periods: all HCU before 1-month after second vaccination and all HCU between 1-month after second vaccination and study end.

Frequency table on the use of medication for COPD (or AECOPD) and type (Chronic use for COPD, Chronic use for other disorders, exacerbation rescue medication) during entire study period will be presented overall and by vaccine group.

Medications will be coded using the GSKDRUG dictionary and frequencies table by GSKDRUG code will be also reported for entire study period, overall and by vaccine group.

As for HCU frequency tables will be presented also for the two sub-periods: before 1-month after second vaccination and after 1-month after second (until study completion).

6.6.3. Lung function and biomarkers

Pre- and post-bronchodilator spirometry

Pre- and post-bronchodilator spirometry assessments will be done at the Screening Visit (pre Day 1), Visit 6 (Day 271) and at Visit 8 (Day 451).

The following pulmonary function parameters will be evaluated:

- Forced Expiratory Volume in 1 second (L): **FEV_1**
- Forced Expiratory Volume in 1 second percent of predicted (%): **FEV_1PP**
- Forced Vital Capacity (L): **FVC**
- Forced Vital Capacity percent of predicted (%): **FVCPP**
- FEV_1 and FVC ratio: **FEV_1/FVC**
- Peak Expiratory Flow (L/sec): **PEF**
- Forced expiratory flow between 25% and 75% of FVC (L/sec): **$FEF_{25-75\%}$**
- FEF between 25-75% of FVC percent of predicted(%): **$FEF_{25-75\%}$PP**

Descriptive analysis (N, mean, SD, median, min and max) on all spirometric measurements at each time point.

Biomarkers

The following selected biomarkers will be evaluated at Day 1 and Day 451 and at each AECOPD visit: fibrinogen, hsCRP and IP-10.

Descriptive statistics (N, mean, SD, median, min and max) will be tabulated for each biomarker and at each time point.

6.6.4. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate humoral immune responses to vaccination and efficacy (i.e., reduction in AECOPD). Details of the methodologies will be included in ad hoc SAP for this purpose.

7. ANALYSIS INTERPRETATION

The primary objective analysis (efficacy) of this study will be evaluated at alpha error of 13% (two-sided test) which is the measurement of the accuracy of our estimation.

Also 2-sided 95% CIs will be provided to show the precision of estimation.

For the secondary objectives we have the following:

- Inferential analyses for efficacy are planned to be performed at alpha level of 0.13 (two sided). No alpha adjustment for multiple testing in the secondary endpoints will be performed, nevertheless the 2-sided 95% CIs will be also provided
- All analyses for immunogenicity are planned to be performed at alpha level of 0.05 with no adjustment for multiplicity.

CMI and safety analyses are intended to be descriptively only.

All tertiary objectives are exploratory and a p-value <0.1 is considered as reference for statistical significance in comparative analysis. Those comparisons should be interpreted with caution.

8. CONDUCT OF ANALYSES

The analyses of the primary, secondary and tertiary endpoints will be completed once data are released. They will be finalized at the end of the trial, when all data up to and including Visit 8 (Day 451) will be available and cleaned.

An integrated clinical study report containing all data will be written and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These data will be documented in annex(es) to the study report and will be made available to the investigators at that time.

In addition to the data and analysis for the clinical study report, four safety interim data evaluations will be carried by an internal Safety Review Committee (iSRC).

8.1. Sequence of analyses

The following safety interim analyses performed by iSRC are planned:

First one will be done once 60 subjects complete one month after first vaccination (i.e., the first 60 subjects completed Visit 2-Day 31)

Second one will be done once 60 subjects complete one month after second vaccination (i.e., the first 60 subjects completed Visit 4- Day 91)

Third one will be done once 300 subjects complete one month after first vaccination (i.e., the first 300 subjects completed Visit 2- Day 31)

Fourth one will be done once 300 subjects complete one month after second vaccination (i.e., the first 300 subjects completed Visit 4- Day 91)

Table 9 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
60 subj safety post dose 1	E1_02	Internal	N	N	See SRT column in TOC
60 subj safety post dose 2	E1_03	Internal	N	N	See SRT column in TOC
300 subj safety post dose 1	E1_04	Internal	N	N	See SRT column in TOC
300 subj safety post dose 2	E1_05	Internal	N	N	See SRT column in TOC
All data analysis	E1_01	Study report	Y	Y	All tables in final TOC

8.2. Statistical considerations for interim analyses

Four (unblinded) interim analyses to evaluate the safety during the exposure period will be conducted. These analyses will be performed by an internal Safety Review Committee (iSRC) and in the study team will not be part of the vaccine unblinded review of safety data.

The iSRC will conduct *unblinded* reviews of all available safety data from the present study while taking into account any other findings that could have an impact on the safety of the subjects, and will determine whether there is a safety signal that needs to be escalated to GSK Biologicals' Vaccines Safety Monitoring Board (VSMB). In the event that a safety signal is observed, GSK Biologicals' VSMB might decide to suspend, modify or continue the conduct of the study.

Before each iSRC safety evaluation in this study, the SRT will review the same safety data, but in a ***blinded*** manner.

In addition to the planned iSRC (and SRT) evaluations, *ad hoc* safety evaluations can take place if a safety concern is identified by an investigator or by the SRT.

Interim analysis unblinded data will not be circulated outside of the iSRC team and no individual clinical study report will be written as a result of these safety evaluations.

The planned interim analyses are only for safety monitoring. No conclusions on efficacy, immunogenicity or other endpoints will be carried out, thus no alpha adjustment will be performed.

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 analyses and their role (synopsis, in-text, post-text, 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.

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.

Jones PW, Quirk FH, and Baveystock CM. “The St. George's Respiratory Questionnaire.” *Respiratory Medicine* 1991. 85(Suppl. B):25-31.

Liang KY, and Zeger SL. “Longitudinal Data Analysis Using Generalized Linear Models.” *Biometrika* 1986; 73:13-22.

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

Newcombe RG. “interval estimation for the difference between independent proportions: comparison of eleven methods” *Statistics in Medicine* 1998; 17: 873-890.

White SJ, Freedman LS. “Allocation of patients to treatment groups in a controlled clinical study”. *Br J Cancer* 1978; 37: 849-857.

Wilkinson TMA, et al. A prospective observational cohort study of the dynamics of airway pathogens and the seasonal aetiology of exacerbations in chronic obstructive pulmonary disease” *Thorax 2017;0:1–9. doi:10.1136/thoraxjnl-2016-209023).*

Handling missing efficacy data:

Efficacy – Clinical Endpoint

Missing or non-evaluable measurements will not be replaced.

Efficacy – Bacteriological Endpoint

For a given subject and a given bacteriological measurement, missing or unevaluable measurements will not be imputed.

Subjects who did not have any sputum collected or have missing measurements at all AECOPD (if at least 1 AECOPD occurred) will not be taken into account for the NTHi and/or Mcat-associated AECOPD analyses.

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI *[Clopper, 1934]*.

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the paper from Robert G. Newcombe: interval estimation for the difference between independent proportions: comparison of eleven methods (Newcombe, 1998). The standardised asymptotic method used is the method six.

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 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.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which injection occurred. More specifically dose 1 refers to all injections administered at the first vaccination visit (Visit 1) while dose 2 corresponds to all injections administered at the second vaccination visit (Visit 3) 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.

- The number of doses for a product is the number of time the product is 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 Kilogramm= weight in Pounds / 2.2

  – Weight in Kilogramm =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 (ie 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

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)

- Exacerbations in previous 12 months

Data will be categorized as following:

1. AECOPDs in the last 12 months managed without oral corticosteroids and antibiotics ='Mild'
2. AECOPDs in the last 12 months that required oral corticosteroids and/or antibiotics ='Moderate'
3. AECOPDs in the last 12 months that required hospitalization='Severe'

11.2.4. Efficacy

- **AECOPD events**: AECOPD events are confirmed according to investigator judgment after an AECOPD visit which is aimed to exclude worsening in symptoms not related to an AECOPD event.

eDiary alerts refer to daily symptoms recorded the morning after (also called morning symptoms). Alerts are based on the Anthonisen criteria:

- Worsening of two or more of the following major symptoms for at least two consecutive days*: dyspnea, sputum volume, sputum purulence (color)

Or

- Worsening of any major symptom together with any of the following minor symptoms for at least two consecutive days*: sore throat, cold (nasal discharge and/or nasal congestion), fever (oral temperature $\geq 37.5°C$) without other cause, increased cough, increased wheeze.

** The same two symptoms do not have to be present on both days as long as at least one major symptom is present on both days.*

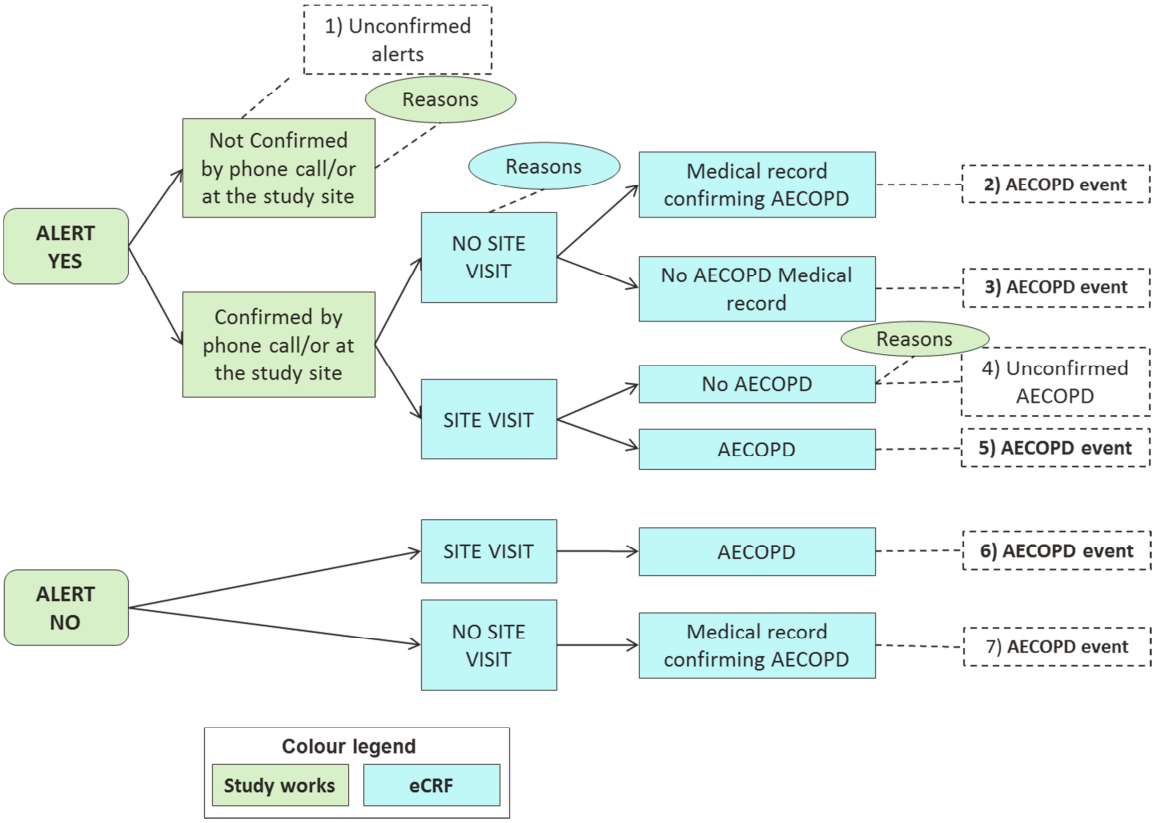
AECOPD visits are scheduled after an electronic Diary Card alert confirmed by the investigator (by phone call or at the study site) or after spontaneous site visits due to worsening symptoms without any alert.

Potential AECOPD will be confirmed and registered as AECOPD event based on the following scheme:

- eDiary ALERT + phone call no confirmed = NO AECOPD event
- eDiary ALERT + phone call confirmed + site visit confirmed = AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no confirmed = NO AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no performed + Medical record confirmed = AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no performed + Medical record no confirmed = NO AECOPD event.

- eDiary ALERT + phone call confirmed + site visit NO performed + Medical record no available = AECOPD event.
- eDiary NO ALERT + site visit NO confirmed = NO AECOPD event.
- eDiary NO ALERT + site visit confirmed = AECOPD event.
- eDiary NO ALERT + site visit NO performed + Medical record confirmed = AECOPD event.
- eDiary NO ALERT + site visit NO performed + Medical record no available/no confirmed = NO AECOPD event

Figure 2 AECOPD assessment



- **AECOPD onset date**: AECOPD onset will be defined as the first day of the two consecutive days of worsening symptoms.
- **AECOPD recovery date:** AECOPD recovery will be determined / confirmed by the investigator/delegate during (a) follow-up phone call(s) which will take place every 2 weeks until the AECOPD has resolved. The end date will be based on when the investigator/delegate determines that the AECOPD symptoms have resolved. In determining this end date, consideration will be given to symptoms recorded in the electronic Diary Card and patient assessment during the phone calls.

- **AECOPD duration** will be defined as the number of days from AECOPD onset (included) and AECOPD recovery (not included).

  Duration = date2 – date1,

  with date2: AECOPD recovery date,

  date1: AECOPD onset date

- **Unconfirmed AECOPD event with morning e-diary signal alert notification:** An alert from the electronic Diary Card not confirmed to be an AECOPD after contact by phone call or at the study site.
- **Grading of severity of an exacerbation:** Severity of exacerbations is defined as per protocol:
  - Mild: Worsening symptoms of COPD that are self-managed by the patient.
  - Moderate: Worsening symptoms of COPD that require treatment with oral corticosteroids and/or antibiotics.
  - Severe: Worsening symptoms of COPD that require treatment with in-patient hospitalisation or home care intervention.

Severity of the exacerbation will not be derived but taken directly from the information entered in the CRF (i.e. Severity of exacerbation will be taken from the conclusion of the exacerbation visit).

11.2.5. 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/Titres (GMC/Ts) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres 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 GMT calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol (see also Table 2 on section 6.4.1).
- 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.
- 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.

11.2.6. 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 adverse events within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited adverse events based on the Total Vaccinated Cohort (TVC) 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.
- All solicited adverse events will be considered probably related to study vaccine.

Unsolicited adverse events: 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 adverse event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

- Unsolicited AE will be classified in the e-CRF as possibly related to study vaccine (YES or NO), based on the PI judgment.
- The related dose for an event (e.g., AE, medication, vaccination,…) is the study dose given before an event. In case the event takes place on a day a study dose is given, the related dose will be that of the study dose even if the event actually took place before. For instance, for a conc. medication started on the day of study dose 2 but before dose 2 administrations, the related dose will be dose 2.

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.

Table 10 Denominator for safety tables

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Solicited general adverse event	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 adverse event	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 adverse event	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
Concomitant vaccination	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.

Table 11 Number of decimals per parameter

Parameters	Number of decimal digits
% of count, including LL & UL of CI	1
p-value	3
Mean, median	Number of decimals in the raw data + 1
SD	Number of decimals in the raw data + 2
Minimum, maximum, range	Number of decimals in the raw data

LL = Lower Limit UL = Upper Limit CI = Confidence Interval
SD = Standard deviation

11.2.7. Other endpoints

Sputum quality criteria

The following criteria and scores will be used:

- >25 squamous epithelial cells/field → sample of bad quality
- 10-25 squamous epithelial cells/field →sample of moderate quality
- < 10 squamous epithelial cells/field → sample of good quality

11.3. Randomization method and minimization algorithm

Subjects are randomised using a centralised randomisation system on internet (SBIR) at first dose. The system incorporates a minimization alogorithm based on White SJ and Freedam LS method (White, 1978) and it is described below:

Notation:

- k input values to be used for minimization, each with a weight w_k (k=1,.., K) and l_k variants.
- i treatment groups applicable to stratum the subject has been identified with randomization ratio a_1,… a_i
- D: percentage of determinism
- W: weight assigned to each minimization factor

In this study k=4: Country, GOLD grade, History of exacerbation and Age group defined as:

COUNTRY [8 variants]: BE CA FR DE IT ES UK US

GOLD [3 variants]: 2 3 4

AGECAT [2 variants]: 40-60 61-80

HIST_ES [2 variants]: < 2 >=2

i=2: VACCINE and PLACEBO with randomization ratio 1:1 (a_i=1)
D=90%
W=1 for each variable

Algorithm:

For a new subject in criteria levels $s_1 \ldots s_k$

Step 1: Minimization computation

Step 1.1: Initialize Problem flag to 0

For each criteria variants s_k, compute the number of subjects already enrolled in each treatment within the strata dedicated to the subject.

Let b_{ik} the number for treatment i & criteria variant k: b_{ik} is the total number of subjects already randomized (excluding subjects cancelled/withdrawn prior dose 1) in treatment i and in criteria variant k within the strata dedicated to the subject.

Step 1.2: For each treatment i: compute Ai = 1/ai * sumk(w_k*b_{ik})

Step 2: determine whether the algorithm is random or determinist:

Generate R, a random number within [0-1], uniform distribution

Step 3: check determinism

If R < % determinism, go to step 4 (determinism) else go to step 5 (random)

Step 4: determinism

4.1: Identify all treatments with the lowest value Ai

4.2: Select randomly one of the treatments identified in step 4.1, let it be T. Go to step 6, if no more treatment then randomization failed

Step 5: randomization

Select randomly one of the treatments dedicated to subject's strata, let it be T. Go to step 6, if no more treatment then randomization failed.

Step 6: treatment allocation

Assign one of the treatment number. related to treatment T in the subject's center.

If no treatment number. related to treatment T is available in the subjects center, then go & repeat step 4 (determinism) or 5 (random) while dropping treatment T (set problem flag=1).

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

13.1. Lay-out for posting

Template 1A Number of enrolled subjects by country *by using %FREQ_DIS*

		10-10-3-AS N=300	PLACEBO N=300	Total N =600
Characteristics	**Age Categories**	**n**	**n**	**n**
France	40-59 years			
	60-80 years			
	Total			
Germany	40-59 years			
	60-80 years			
	Total			
xxx	40-59 years			
	60-80 years			
	Total			

N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories

Template 2A Number of enrolled subjects by age category by using %FREQ_DIS

		10-10-3-AS N=300	PLACEBO N=300	Total N =600
Characteristics	**Categories**	**n**	**n**	**n**
Age category	In utero			
	Preterm newborn infants (gestational age < 37 wks)			
	Newborns (0-27 days)			
	Infants and toddlers (28 days-23 months)			
	Children (2-11 years)			
	Adolescents (12-17 years)			
	Adults (18-64 years)			
	From 65-84 years			
	85 years and over			
	Missing			

N = Number of enrolled subjects
n = number of enrolled subjects included in each group or in total for a given age category or for all age categories

Template 3A Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort) *by using %DROPSUM (OTH=0) Macro:*

	10-10-3-AS	PLACEBO	Total
Number of subjects vaccinated			
Number of subjects completed			
Number of subjects withdrawn			
Reasons for withdrawal :			
Serious Adverse Event			
Non-Serious Adverse Event			
Eligibility criteria not fulfilled (inclusion and exclusion criteria)			
Protocol violation			
Consent withdrawal (not due to an adverse event)			
Migrated/moved from study area			
Lost to follow-up (subjects with incomplete vaccination course)			
Lost to follow-up (subjects with complete vaccination course)			
Sponsor study termination			
Others			

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not complete their last visit

Template 4A Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion *by using %ELIMLIST*

Number of subjects enrolled into the study as well as the number excluded from ATP analyses at Day 21 with reasons for exclusion									
	Total			**10-10-3-AS**		**PLACEBO**		**NOGRP**	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**

Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Template 5A Number (%) of subjects with serious adverse events from the Day 1 till end of the study *by using new CTR_SAE Macro:*

Type of Event	Primary System Organ Class	Preferred Term (CODE)	10-10-3-AS N = 300			PLACEBO N = 300		
			n*	n	%	n*	n	%
SAE	At least one symptom							
	<each SOC>	<each PT>						
Related SAE	At least one symptom							
	<each SOC>	<each PT>						
Fatal SAE	At least one symptom							
	<each SOC>	<each PT>						
Related Fatal SAE	At least one symptom							
	<each SOC>	<each PT>						

N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 6A Solicited and unsolicited symptoms experienced by at least 5 % of subjects, classified by MedDRA Primary System Organ Class and Preferred Term including number of events reported - SAE excluded *by using %UNSOL (NIH=5, EVENT=1)*

		10-10-3-AS N = 300			PLACEBO N = 300		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
At least one symptom							
<each SOC>	**<each PT term>**						

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

13.2. Lay-out for CSR

Template 1 Overview of Sets Analyzed

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	n	%	n	%	n	%
All Enrolled set	xxx	100%	xxx	100%	xxx	100%
mTVC	xxx	xx%	xxx	xx%	xxx	xx%
mTVC-PCR	xxx	xx%	xxx	xx%	xxx	xx%
mTVC-Culture	xxx	xx%	xxx	xx%	xxx	xx%
TVC (Exposed Set)						
TVC-Efficacy	xxx	xx%	xxx	xx%	xxx	xx%
TVC-Immunogenicity	xxx	xx%	xxx	xx%	xxx	xx%
TVC-CMI	xxx	xx%	xxx	xx%	xxx	xx%
TVC-Safety	xxx	xx%	xxx	xx%	xxx	xx%
ATP (PPS)						
ATP- Efficacy (clinical)	xxx	xx%	xxx	xx%	xxx	xx%
ATP- Efficacy (bacteriological)	xxx	xx%	xxx	xx%	xxx	xx%
ATP- Immunogenicity	xxx	xx%	xxx	xx%	xxx	xx%
ATP- CMI	xxx	xx%	xxx	xx%	xxx	xx%

<group description >
n = number of subjects included in each group or in total
% = n/All x 100

Template 2 Study Termination

	10-10-3-AS		PLACEBO		Total	
	n	%	n	%	n	%
Number of subject screened	xxx		xxx		xxx	
Number of subject enrolled	xxx		xxx		xxx	
Number of subject exposed	xxx	xx%	xxx	xx%	xxx	xx%
Number of subject completed	xxx	xx%	xxx	xx%	xxx	xx%
Number of subject withdrawn	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for withdrawn						
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%

<group description >
n = number of subjects included in each group or in total
% = n/All x 100

Template 3 Study Termination, by visit

	10-10-3-AS		PLACEBO		Total	
	n	%	n	%	n	%
Number of subject screened	xxx		xxx		xxx	
Number of subject enrolled	xxx		xxx		xxx	
Number of subject exposed dose 1	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit 1	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation						
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit 2	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation	xxx	xx%	xxx	xx%	xxx	xx%
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
Total number of subject exposed dose 2	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit 3	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation	xxx	xx%	xxx	xx%	xxx	xx%
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit x	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation	xxx	xx%	xxx	xx%	xxx	xx%
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
…..	xxx	xx%	xxx	xx%	xxx	xx%

<group description >
n = number of subjects included in each group or in total
% = n/All x 100

Template 4 Demographic and Baseline Characteristics (and Vital Signs)

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at enrolment (Years)	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-
Age Group	40-59 years	xx	xx.x				
	60-80 years	xx	xx.x				
Gender	Female	xx	xx.x	xx	xx.x	xx	xx.x
	Male	xx	xx.x	xx	xx.x	xx	xx.x
Race	Black or African American	xx	xx.x	xx	xx.x	xx	xx.x
	American Indian or Alaska Native	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - Central / South Asian Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - East Asian Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - Japanese Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - South East Asian Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Native Hawaiian or Other Pacific Islander	xx	xx.x	xx	xx.x	xx	xx.x
	White - Arabic / North African Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	White - Caucasian / European Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Other	xx	xx.x	xx	xx.x	xx	xx.x
Ethnicity	Hispanic or Latino	xx	xx.x	xx	xx.x	xx	xx.x
	Not Hispanic nor Latino	xx	xx.x	xx	xx.x	xx	xx.x
Exacerbations in previous 12 months	Total AECOPD	xx	xx.x	xx	xx.x	xx	xx.x
	Mild	xx	xx.x	xx	xx.x	xx	xx.x
	Moderate	xx	xx.x	xx	xx.x	xx	xx.x
	Severe	xx	xx.x	xx	xx.x	xx	xx.x
Exacerbations in previous 12 months category	>2	xx	xx.x	xx	xx.x	xx	xx.x
	>=2	xx	xx.x	xx	xx.x	xx	xx.x
Smoking status	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Pack year	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-
GOLD grade	Grade 1	xx	xx.x	xx	xx.x	xx	xx.x
	Grade 2	xx	xx.x	xx	xx.x	xx	xx.x
	Grade 3	xx	xx.x	xx	xx.x	xx	xx.x
	Grade 4	xx	xx.x	xx	xx.x	xx	xx.x
FE1/FVC	>=70	xx	xx.x	xx	xx.x	xx	xx.x
	>70	xx	xx.x	xx	xx.x	xx	xx.x
CMI sub-cohort	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Culture cohort	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation

Note: similar of the above tables is for vital sign but with different parameters (see section 6.1.1)

Template 5 Number of Subject by Country, Center and within CMI and Sputum culture subsets

					Sputum Culture Subset				CMI Subset			
	10-10-3-AS	PLACEBO	Total		10-10-3-AS	PLACEBO	Total		10-10-3-AS	PLACEBO	Total	
Center	**n**	**n**	**n**	**%**	**n**	**n**	**n**	**%**	**n**	**n**	**n**	**%**
France												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Germany												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Belgium												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Italy												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxx												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
……	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total												
	xx	xx	xx	100%	xx	xx	xx	100%	xx	xx	xx	100%

<group description >
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100

Template 6 Medical History History

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
System Organ Class Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
SOC 1						
PT 1						
PT 2						
PT 3						
……						
SOC 2						
PT 1						
PT 2						
PT 3						
…..						
SOC 3						
…….						

<group description >
N = number of subjects
n = number of subjects in a given category
SD=Standard Deviation

Template 7 Vaccination History History

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	n	**%**	**n**	**%**	**n**	**%**
Any influenza and/or pneumococcal vaccination						
Influenza vaccination						
pneumococcal vaccination						

<group description >
N = number of subjects
n = number of subjects in a given category
SD=Standard Deviation

Template 8 Vaccine Administration

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Prevaccination temperature (C°)	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-
Temperature location	xxxxx	xx	xx.x				
	xxxxxx	xx	xx.x				
Vaccination Administered	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Vaccination Site	xxxxx	xx	xx.x	xx	xx.x	xx	xx.x
	xxxxxx	xx	xx.x	xx	xx.x	xx	xx.x
	xxxxxx	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation

Template 9 Days on which vaccinations occurred

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Vaccination 1	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Vaccination 2	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Vaccination 2: Days post first vaccination	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation

Template 10 Days of Blood Samples at Scheduled Visit

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Visit 1 - Day 1						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample Haematology	xx	xx.x	xx	xx.x	xx	xx.x
Visit 2 - Day 31						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	0	0	0	0	0	0
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 31 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 30-45 Days Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 30-45 Days Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Visit 3 - Day 61						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	0	0	0	0	0	0
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 61 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 60-75 Days from Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 60-75 Days from Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Visit 4 - Day 91						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 91 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 30-45 Days from Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 30-45 Days from Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Visit 6 - Day 271						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 271 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 180-210 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 180-210 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 8 - Day 451						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample Haematology	0	0	0	0	0	0

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Timing of study day 451 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 360-390 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 360-390 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 11 Days of Sputum Samples at Study Visit

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Visit 1 - Day 1						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Visit 4 - Day 91						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 91 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 30-45 Days Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 30-45 Days Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Visit 5 - Day 181						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 181 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 90-120 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 90-120 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 6 - Day 271						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 271 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 180-210 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 180-210 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 7 - Day 361						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 361 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 270-300 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 270-300 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 8 - Day 451						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Timing of study day 451 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 360-390 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 360-390 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 12 Duration of Subject participation in the Study

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Overall duration of subjects participation (days)	n						
	Mean	xx	xx.x	xx	xx.x	xx	xx.x
	Median	xx	xx.x	xx	xx.x	xx	xx.x
	SD						
	Minimum	xx	xx.x	xx	xx.x	xx	xx.x
	Maximum	xx	xx.x	xx	xx.x	xx	xx.x
Overall duration (days)	<31 days	xx	xx.x	xx	xx.x	xx	xx.x
	31 – <91 days	xx	xx.x	xx	xx.x	xx	xx.x
	91 – <181 days	xx	xx.x	xx	xx.x	xx	xx.x
	181 - <271 days	xx	xx.x	xx	xx.x	xx	xx.x
	361 - <361 days	xx	xx.x	xx	xx.x	xx	xx.x
	361 – <451 days	xx	xx.x	xx	xx.x	xx	xx.x
	>=451 days	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 13 Protocol deviation summary /exclusion summary

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Any protocol deviation	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 1	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 2	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 3	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 4	xx	xx.x	xx	xx.x	xx	xx.x
……	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Note: similar of the above tables is for Exclusion with each population in raw before the list of exclusions

Template 14 Percentage of subjects with antibody concentration above assay cut-off and vaccine group differences

		10-10-3-AS N=300				PLACEBO N=300				Difference N=600	
Strain	**Time**	N	n	%	95% CI	N	n	%	95% CI	%	95% CI
Anti – PD Antibody > 153	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
Anti – PE Antibody > 8	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
Anti – PilA Antibody > 7	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
Anti – USPA 2 igG Antibody > 18	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 15 Geometric mean Antibody concentration and Vaccine Ratios

		10-10-3-AS N=300		PLACEBO N=300		GMTs Ratio N=600	
Time	**Parameters**	**Value or n**	**95% CI**	**Value or n**	**95% CI**	**Value or n**	**95% CI**
Day 1 (Pre dose)	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 31	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 61 (Pre dose)	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 91	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 271	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 451	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-

<&footnote1.>
<group description >
GMC = geometric mean antibody concentration
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
CI=Confidence interval

Template 16 Geometric mean Ratio and Vaccine Ratios

		10-10-3-AS N=300		PLACEBO N=300		GMRs Ratio N=600	
Time	**Parameters**	**Value or n**	**95% CI**	**Value or n**	**95% CI**	**Value or n**	**95% CI**
Day 31 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 61 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 91 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 271 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 451 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-

<&footnote1.>
<group description >
GMR = geometric mean antibody concentration ratio
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
CI=Confidence interval

Template 17 Descriptive statistics of PD, PE, PilA, UspA2 specific CD4+ T cells expressing at least <two markers> per million cells, using background reduced frequency data

			10-10-3-AS N=	PLACEBO N=
Simulation	**TIMING**	**Parameters**	**Value**	**Value**
Hi NTHi PD	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
Hi NTHi PE	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx

			10-10-3-AS N=	PLACEBO N=
Simulation	**TIMING**	**Parameters**	**Value**	**Value**
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
Hi NTHi PilA	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		n	xx	xx

			10-10-3-AS N=	**PLACEBO N=**
Simulation	**TIMING**	**Parameters**	**Value**	**Value**
M catarrhalis UspA2	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		n	xx	xx

<&footnote1.>
<group description >
N = number of subjects
Value = value of the considered parameter
SD = Standard deviation
Q1,Q3 = First and third quartiles

Template 18 Summary of the number of < type>AECOPD

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		xxx				
Exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		xxxx				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 19 Summary of the number of AECOPDs by severity

				10-10-3-AS N=		PLACEBO N=	
Severity	**Timings**			**Value or n**	**%**	**Value or n**	**%**
Mild	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
Moderate	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				

				10-10-3-AS N=		PLACEBO N=	
Severity	**Timings**			**Value or n**	**%**	**Value or n**	**%**
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
Severe	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				

				10-10-3-AS N=		PLACEBO N=	
Severity	**Timings**			**Value or n**	**%**	**Value or n**	**%**
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
Overall total	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 20 Vaccine Efficacy for <type> AECOPDs

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**Time (year)**	**n/T**	**87% CI**	**95% CI**	**%**	**87% CI**	**95% CI**	**P-Value**
<Moderate and severe> AECOPDs	10-10-3-AS01E										
	PLACEBO										

<&footnote1.>
<group description >
n = number of subjects in a given category
Time (year) = sum of follow-up period expressed in year
n/T = person-year rate in each group

Template 21 Parameter estimation following Vaccine Efficacy of <type> AECOPDs

Covariate	Estimate	95% CI	P-Value
Country			
Age			
GOLD			
Exacerbation History			

<&footnote1.>

Template 22 Summary of the number of < type>AECOPD, by sub-period

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
Any exacerbation after 1 month post Dose 2 until month 4	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
Any exacerbation before 1 month post Dose 2 until month 7	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Any severity exacerbation after 1 month post Dose 2 until month 10	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 23 Average length of <type> AECOPD

		10-10-3-AS N=	PLACEBO N=
Timings	**Statistics**	**Value**	**Value**
Any exacerbation before 1 month post Dose 2	N		
	Mean		
	SD		
	Median		
	Q1		
	Q3		
	Minimum		
	Maximum		
Any exacerbation after 1 month post Dose 2	N		
	Mean		
	SD		
	Median		
	Q1		
	Q3		
	Minimum		
	Maximum		

<group description >
N = number of exacerbations with calculated duration in a given category
Value = value of the considered parameter, SD = Standard deviation

Template 24 Average length of <type> AECOPD, by Severity

			10-10-3-AS N=	PLACEBO N=
Exacerbation severity	**Timings**	**Statistics**	**Value**	**Value**
Mild	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
Moderate	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
Severe	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		

			10-10-3-AS N=	PLACEBO N=
Exacerbation severity	**Timings**	**Statistics**	**Value**	**Value**
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
Any severity exacerbations	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		

<group description >
N = number of exacerbations with calculated duration in a given category
Value = value of the considered parameter
SD = Standard deviation

Template 25 Hazard Rate for <type> AECOPD

Parameter	DF	Parameter Estimate	SE	P-value	Hazard Ratio
Vaccine group					
Age					
GOLD					
History of AECOPD					

<Parameters description >
DF = degree of freedom
SE = standard error

Template 26 Proportion of Patients with Sputum Samples Positive for Bacterial Pathogens at any stable or exacerbation visit

		10-10-3-AS N=						**PLACEBO N=**					
		Patients			Sputum positive			Patients			Sputum positive		
Bacteria	Visit	N	n	%	ns	%	95% CI	N	n	%	ns	%	95% CI
Any	Enrolment												
	Any stable visit												
	Any AECOPD visit												
H. influenzae	Enrolment												
	Any stable visit												
	Any AECOPD visit												
M. catarrhalis	Enrolment												
	Any stable visit												
	Any AECOPD visit												
S. pneumoniae	Enrolment												
	Any stable visit												
	Any AECOPD visit												
S. aureus	Enrolment												
	Any stable visit												
	Any AECOPD visit												
P. aeruginosa	Enrolment												
	Any stable visit												
	Any AECOPD visit												
K. pneumoniae	Enrolment												
	Any stable visit												
	Any AECOPD visit												
A. baumannii	Enrolment												
	Any stable visit												
	Any AECOPD visit												

N = number of patients in each visit
n= number of patients positive to bacteria
% = percentage of patients with sputum samples positive for bacterial pathogens
ns = number of sputum samples positive to bacteria

Template 27 Subjects with at least one Solicited Adverse Events

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
Dose 2	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
Overall/dose	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
Overall/subject	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

<group description >
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 28 Subjects with Solicited Local Adverse Events, Maximum Event Severity and Grade 3 Events

		10-10-3-AS					PLACEBO				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										
Dose 2											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										
Overall/dose											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										
Overall/subject											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										

<group description >
For each dose and overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Same lay-out for General symptoms (see section 6.5.1.1 for list for local or general solicited adverse events)

Template 29 Body Temperature Measurements - Maximum Event Severity From Day 1 Through Day 7 Following each Vaccination

		10-10-3-AS					PLACEBO				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Temperature/(Oral) (°C)	<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										
Dose 2											
Temperature/(Oral) (°C)	<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										
Overall/dose											
Temperature/(Oral) (°C)	<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										
Overall/subject											
Temperature/(Oral) (°C)	<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										

<group description >
For each dose and overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses

n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 30 Concomitant Medication and Vaccination

	10-10-3-AS N=		PLACEBO N=	
Generic Drug Name	**n**	**%**	**n**	**%**
Term 1				
Term 2				
Term 3				
Term 4				
xxxx				

<group description >
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

Template 31 Subjects With Unsolicited Adverse Events After Any Vaccination sorted by SOC

		10-10-3-AS N=		PLACEBO N=	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**n**	**%**
At least one Adverse Event					
SOC 1	PT 1				
	PT 2				
	PT 3				
SOC 2	PT 1				
	PT 2				
	PT 3				
SOC 3	PT 1				
	PT 2				
	PT 3				

<group description >
At least one symptom = at least one Adverse Event experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

Template 32 Number and Percentage of sputum samples per quality score, collected at each Stable and Exacerbation visit

		10-10-3-AS N=		PLACEBO N=	
Visit	Quality	n	%	n	%
Visit 1 (Day 1)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
Visit 4 (Day 91)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
Visit 5 (Day 181)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
Visit x (Day xx)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
AECOPD Visit 1	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
AECOPD Visit x	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				

<group description >
N= Number of subjects
n = number of sputum
%= percentage of sputum in each category (n/total n)

Template 33 Proportion of Patients with Sputum Samples Positive for Bacterial Pathogens at any stable or exacerbation visit, by Country

		Any stable visit												Any AECOPD visit					
		10-10-3-AS N=						PLACEBO N=						10-10-3-AS N=			PLACEBO N=		
		Patients			Sputum			Patients			Sputum			Patients			Sputum		
Bacteria	Country	N	n	%	ns	sp	%	N	n	%	ns	sp	%	N	n	%	ns	sp	%
Any	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
H. Influenzae	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
M. catarrhalis	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
S. pneumoniae	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
xxx	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		

<group description >
N = number of patients in each visit
n= number of patients positive to bacteria
% = percentage of patients with sputum samples positive for bacterial pathogens
ns = number of sputum samples
np= number of sputum samples positive to bacteria

Template 34 Proportion of patients with sputum samples positive for bacterial pathogens by visit.

		10-10-3-AS N=				PLACEBO N=			
Bacteria	Visit / Day	N	n	%	95% CI	N	n	%	95% CI
Any	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD Visit 3								
	AECOPD >3								
. H. Influenzae	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD 3								
	AECOPD >3								
M. catarrhalis	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD Visit 3								
	AECOPD >3								
S. pneumoniae	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD Visit 3								
	AECOPD >3								
xxx	…..								

<group description >
N = number of patients providing a sputum sample
n = number of sputum samples positive for bacterial pathogen
% = percentage of patients with sputum samples positive for bacterial pathogens

Template 35 Sputum sample collection, by method

		Day 1				Day 91				Day x			
		10-10-3-AS N=		**PLACE N=**		**10-10-3-AS N=**		**PLACE N=**		**10-10-3-AS N=**		**PLACE N=**	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Has a sputum sample collected?	NO												
	YES												
How was the sputum collected?	Spontaneous												
	Induced 0.9%												
	Induced 3%												
Was an antibiotic administered before sputum sample collection?	NO												
	YES												
Number of hours since start of antibiotic administration	Mean												
	SD												
	Median												
	Q1												
	Q3												
	Minimum												
	Maximum												

<group description >
N = number of patients
n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation Q1, Q3 = first and third quartiles

Template 36 Proportion of sputum samples at pre-vaccination, after 2 doses and at any exacerbation visit that are positive for specific pathogens overall and by bacterial species

		10-10-3-AS N=					PLACEBO N=				
					95% CI					95% CI	
Bacteria	**Timings**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Any	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
H. Influenzae	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
M. catarrhalis	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
S. pneumoniae	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
xxx	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										

<group description >
N = number of sputum samples
n = number of sputum samples in a given category
% = n/Number of sputum samples x 100
Hi = Haemophilus influenza

Template 37 Simultaneous bacterial presence in sputum at pre-vaccination, after 2 doses and at any exacerbation visit

	10-10-3-AS																	
	At pre-vaccination visit			After 2 doses (Day 91)			At Any exacerbation visit before Dose 2			At Any exacerbation visit after Dose 2			At Any exacerbation visit at Day 181			At Any exacerbation visit at Day 271		
Bacterial combination	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Hi																		
Hi+Mcat																		
Hi+Mcat+Sp																		
Hi+Oth																		
Hi+Psa																		
Hi+Sp																		
Hi+Sta																		
Hi+Sta+Oth																		
Mcat																		
Mcat+Oth																		
Mcat+Psa																		
Mcat+Sp																		
Mcat+Sta																		
Oth																		
Psa																		
Psa+Oth																		
Sp																		
Sp+Oth																		
Sta																		
None																		

<group description >
N = number of sputum samples
n = number of sputum samples in a given category
% = n/Number of sputum samples x 100

All visits and same table for control

Template 38 Simultaneous selected bacterial presence in sputum pre-vaccination, after 2 doses and at any exacerbation visit for Hi and Mcat

	10-10-3-AS																	
	At pre-vaccination visit			After 2 doses (Day 91)			At Any exacerbation visit before Dose 2			At Any exacerbation visit after Dose 2			At Any exacerbation visit at Day 181			At Any exacerbation visit at Day 271		
Bacterial combination	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Hi alone																		
Mcat alone																		
Hi or Mcat mixed																		
Other																		
None																		

<group description >
N = number of sputum samples
n = number of sputum samples in a given category
% = n/Number of sputum samples x 100

All visits and same table for control

Template 39 Summary of the number of exacerbations having sputum containing any bacterial pathogens

			10-10-3-AS													
			Any		Hi		Mcat		Sp		Sta		Psa		Other	
Timings			**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Any exacerbation before 1 month post Dose 2	N	Sum														
	Number of AECOPD	Sum														
	Total exposure (days)	Sum														
	Overall AECOPD rate	Mean														
	Exacerbation rate	Mean														
		SD														
		Median														
		Q1														
		Q3														
		Minimum														
		Maximum														
	Number of exacerbations	00														
		01														
		02														
		03														
Any exacerbation after 1 month post Dose 2	N	Sum														
	Number of AECOPD	Sum														
	Total exposure (days)	Sum														
	Overall AECOPD rate	Mean														
	Exacerbation rate	Mean														
		SD														
		Median														
		Q1														
		Q3														
		Minimum														
		Maximum														
	Number of exacerbations	00														
		01														
		02														
		03														
		x														

<group description >
N = Total number of subjects

Same lay-out for the 'by Country' table

Template 40 Frequencies of semi-quantitative bacteriological load

			10-10-3-AS										PLACEBO									
			Any		Hi		Mcat		Sp		xxx		Any		Hi		Mcat		Sp		xxx	
Timings			**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Day 1	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
Day 91	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
Day 181	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
xxxx	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
Exacerbation visit 1	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
xxxxx																						

<group description >

Note: if not enough space the two groups can be split (as lay-out 37, 38 and 39)

Template 41 Use of medication to treat AECOPD

		10-10-3-AS N=		PLACEBO N=	
Type		n	%	n	%
Number of medication	0				
	1				
	2				
	3				
	4				
	>4				
Indication	Chronic use COPD				
	Chronic use Other disorders				
	Exacerbation				
	Rescue medication				
Type of treatment	Concomitant medication				
	Treatment given for COPD (standard of care)				
	Additional treatment for COPD (not standard of care).				

<group description >

Template 42 Percentage of Subjects With Healthcare Utilization

		10-10-3-AS N=		PLACEBO N=	
Characteristics		**Value**	**%**	**value**	**%**
Healthcare Use					
Healthcare Use Frequency	0				
	1				
	2				
	3				
Specific Healthcare Use	General practitioner (not the study doctor)	**			
	Respiratory consultant				
	Other specialist				
	Emergency				
	Pulmonary rehabilitation program				
	Nutrition advice				
Hospitalization		***			
	Intensive Care	****			
	General Ward				

<group description >
n = number of subjects in a given category
Value = value of the considered parameter
*number of subjects who used health care consequently to an exacerbation
** number of subjects who went to the GP consequently to an exacerbation
*** number of subjects who have been hospitalized consequently to an exacerbation
**** number of subjects who have been admitted to intensive care consequently to an exacerbation
%=based on total number of subjects and not subjects in each category

Template 43 Pulmonary function test by Visit

Visit		Screening		Day 271		**Day 451**	
Spirometer Parameter		**10-10-3-AS N=**	**PLACEBO N=**	**10-10-3-AS N=**	**PLACEBO N=**	**10-10-3-AS N=**	**PLACEBO N=**
FEV1 (L)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEV1 (% of predicted)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FVC (L)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FVC (% of predicted)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEV1/FVC	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
PEF(L/sec)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEF25-75%	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEF25-75% (% of predicted)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						

<group description >

n = number of subjects in a given category; SD = Standard deviation,

FEV1 = Forced Expiratory Volume of air in 1 second (L), FVC = Forced Expiratory Vital Capacity (L), PEF= Peak Expiratory Flow (L/sec), FEF25-75%= Forced expiratory flow between 25% and 75% of FVC (L/sec)

Template 44 Descriptive statistics of biomarker

		10-10-3-AS N=	PLACEBO N=
Fibrinogen			
Day 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
Day 451	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 2	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit x	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
hsCRP			
Day 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
Day 451	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		

		10-10-3-AS N=	**PLACEBO N=**
AECOPD Visit 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 2	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit x	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
IP-10.			
Day 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
Day 451	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 2	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		

		10-10-3-AS N=	**PLACEBO N=**
AECOPD Visit x	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		

<group description >
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

Template 45 Daily Report for Solicited Adverse Events

10-10-3-AS							
Vaccination Number	**Category**	**Within 60 Min**	**Day 1**	**Day 2**	**Day …**		**Day 7**
Solicited Local Adverse Event: Pain at injection site							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
2	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Any	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Solicited Local Adverse Event: Redness at injection site							
1	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
2	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
Any	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
Solicited Local Adverse Event: xxx							
1	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
xxxx							

Solicited General Adverse Event: Headache							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
2	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Any	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Solicited General Adverse Event: xxxx							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
xxxx							
PLACEBO							
Solicited Local Adverse Event: Pain at injection site							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
2	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Any	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
xxxx							

<group description >

Template 46 Solicited and Unsolicited Adverse Events

		10-10-3-AS N=				PLACEBO N=			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom									
xxxx									

<group description >
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 47 Solicited and Unsolicited Adverse Events, by Vaccination

		10-10-3-AS N=				PLACEBO N=			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Vaccination 1									
At least one symptom									
xxxx									
Vaccination 2									
xxxxx									

<group description >
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Note: Similar lay-out for the 'by Severity' table

Template 48 Summary of EXACT-pro Average Scores

		10-10-3-AS N=300	PLACEBO N=300	Difference N=600
Timing	**Parameters**	**Average Score**	**Average Score**	**Average Score**
Screening	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*			
Treatment	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*	-	-	
Exacerbation	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*	-	-	
Follow –up:	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*			

<group description >
<&footnote >

Template 49 Summary of <questionnaire> scores

		10-10-3-AS N=300	PLACEBO N=300	Difference N=600
Timing	**Parameters**	**Score**	**Score**	**Score**
Screening	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*	-	-	
Day 271	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*	-	-	
Day 451	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*	-	-	
Any Stable Visit	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*			
Any AECOPD Visit	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*			

		10-10-3-AS N=300	PLACEBO N=300	Difference N=600
Timing	**Parameters**	**Score**	**Score**	**Score**
Difference between Day 271 – screening	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	Maximum			
	p-value**			
Difference between Day 451 – screening	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	Maximum			
	p-value**			

<group description >
<&footnote >

Note 1: For the by Severity and by number table lay-out will include an additional raw for severity or number of AECOPD

Note 2: For the SGRQ-C lay-out will include an additional raw for the component scores

Template 50 Number and Percentage of sputum samples by Neutrophils Cells count, collected at each Stable and Exacerbation visit

		10-10-3-AS N=		PLACEBO N=	
Visit	Quality	n	%	n	%
Visit 1 (Day 1)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
Visit 4 (Day 91)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
Visit 5 (Day 181)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
Visit x (Day xx)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
AECOPD Visit 1	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
AECOPD Visit x	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				

<group description >
N= Number of subjects
n = number of sputum
%= percentage of sputum in each category (n/total n)

Template 51 Bacteria direct smear collected at each Stable and Exacerbation visit

		10-10-3-AS N=		PLACEBO N=	
Visit	Quality	n	%	n	%
Visit 1 (Day 1)	Gram-positive Diplococci				
	Gram-positive Cocci				
	Gram-positive rods Bacilli				
	Gram-negative Cocci				
	Gram-negative Bacilli				
	Yeasts				
	Mycelium				
	Yeasts with Pseudomycelium				
	Mixed flora				
	No bacteria				
	Other				
	Not done				
Visit x (Day xx)	Gram-positive Diplococci				
	Gram-positive Cocci				
	Gram-positive rods Bacilli				
	Gram-negative Cocci				
	Gram-negative Bacilli				
	Yeasts				
	Mycelium				
	Yeasts with Pseudomycelium				
	Mixed flora				
	No bacteria				
	Other				
	Not done				
AECOPD Visit x	Gram-positive Diplococci				
	Gram-positive Cocci				
	Gram-positive rods Bacilli				
	Gram-negative Cocci				
	Gram-negative Bacilli				
	Yeasts				
	Mycelium				
	Yeasts with Pseudomycelium				
	xxxx				
	xxxx				

<group description >
N= Number of subjects
n = number of sputum
%= percentage of sputum in each category (n/total n)

Template 52 Summary of the Number of Moderate and Severe AECOPD During Entire Study Period

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Any exacerbation during entire study period	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 53 Summary of the Number of any AECOPD During Entire Study Period, by severity

			10-10-3-AS N=		PLACEBO N=	
Severity			**Value or n**	**%**	**Value or n**	**%**
Mild	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		…				
Moderate	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		…				
Severe	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		…				

			10-10-3-AS N=		PLACEBO N=	
Severity			**Value or n**	**%**	**Value or n**	**%**
Any Severity	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		….				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 54 Average length of <type> AECOPD During Entire Study Period

		10-10-3-AS N=	PLACEBO N=
Timings	**Statistics**	**Value**	**Value**
Any exacerbation During entire study period	N		
	Mean		
	SD		
	Median		
	Q1		
	Q3		
	Minimum		
	Maximum		

<group description >
N = number of exacerbations with calculated duration in a given category
Value = value of the considered parameter, SD = Standard deviation

Note: similar lay-out for the by severity table, adding column with severity

Template 55 Summary of Baseline Haematology profile

		10-10-3-AS N=	PLACEBO N=
White Blood Cells			
Leukocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Neutrophils	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Lymphocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Eosinophils	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Basophils	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Monocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Red Blood Cells			
Erythrocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Hemoglobin	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		

		10-10-3-AS N=	PLACEBO N=
Platelets	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		

Template 56 Percentage of subjects having Hematology parameter below or above normal ranges

		10-10-3-AS N=	PLACEBO N=
White Blood Cells			
Leukocytes	Below		
	Within		
	Above		
	Total		
Neutrophils	Below		
	Within		
	Above		
	Total		
Lymphocytes	Below		
	Within		
	Above		
	Total		
Eosinophils	Below		
	Within		
	Above		
	Total		
Basophils	Below		
	Within		
	Above		
	Total		
Monocytes	Below		
	Within		
	Above		
	Total		
Red Blood Cells			
Erythrocytes	Below		
	Within		
	Above		
	Total		
Hemoglobin	Below		
	Within		
	Above		
	Total		
Platelets	Below		
	Within		
	Above		
	Total		

<group description >
See Listing 16.2.8.1 for Normal Ranges Definitions

Figure 3 Survival curve, Time to First AECOPD

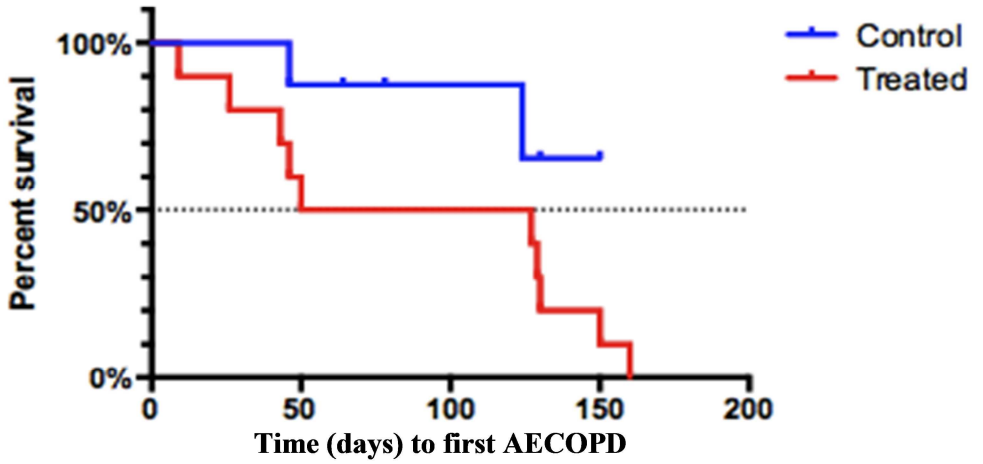


Figure 4 Reverse cumulative distribution curve for <each antigen> antibody concentration before vaccination and one month after the second dose

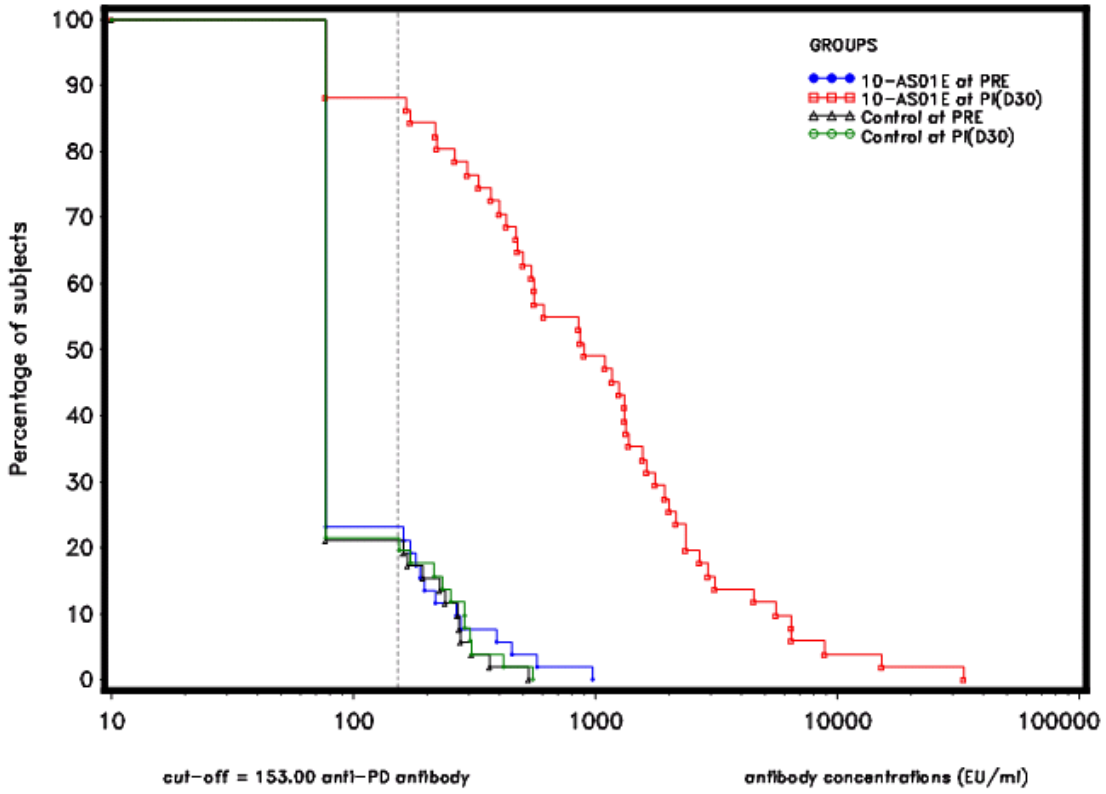


Figure 5 **Box-plots of < each antigen > specific CD4+ T(CD8+T) cells expressing at <specific marker >**

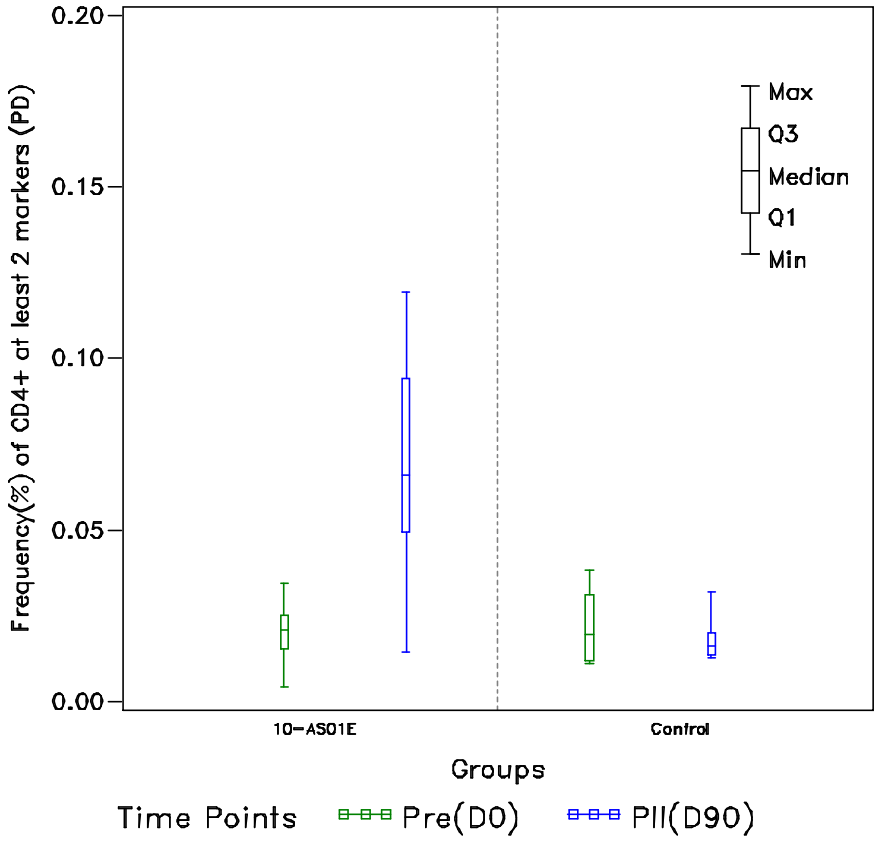


Figure 6 **Pie chart of simultaneous bacterial presence in sputum**

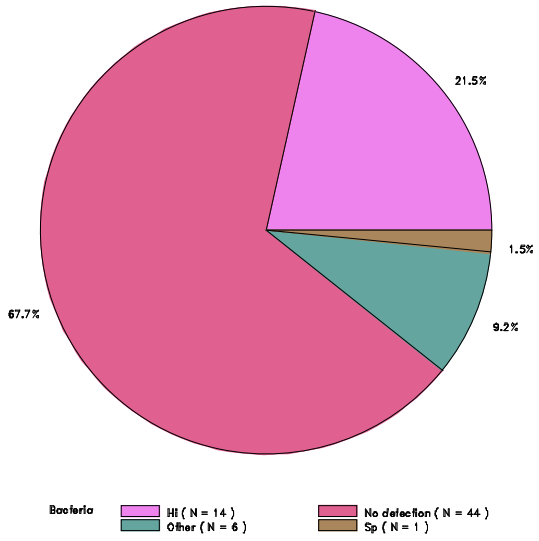


Figure 7 Average Score for EXACT-PRO per each visit period

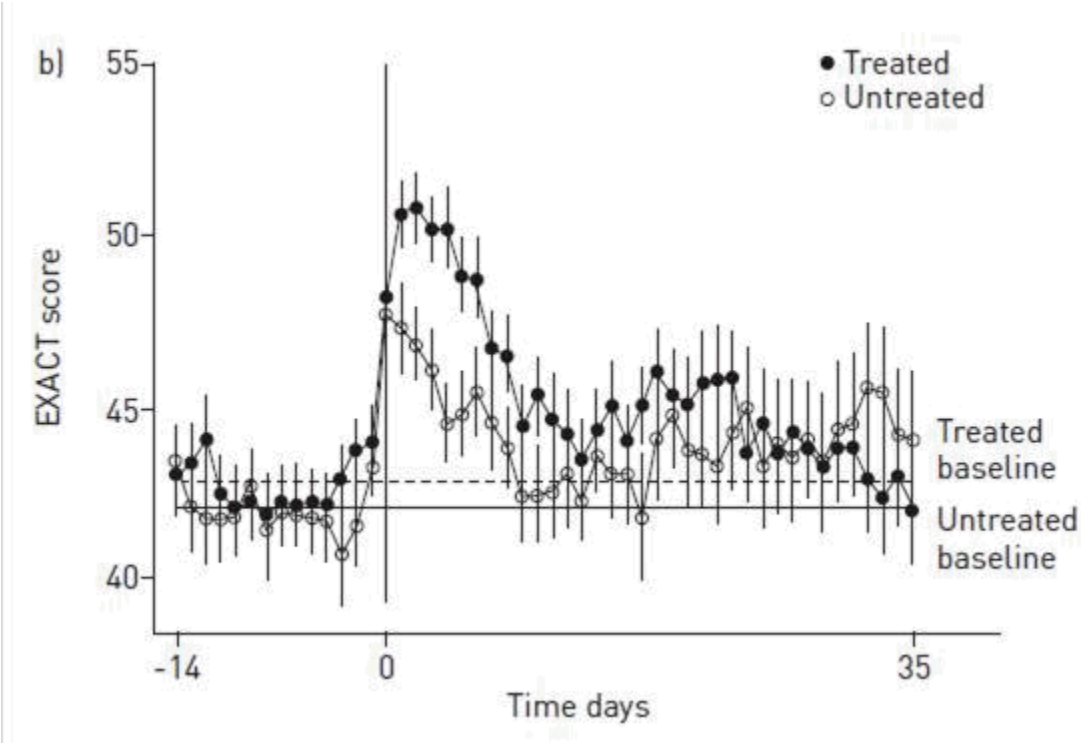
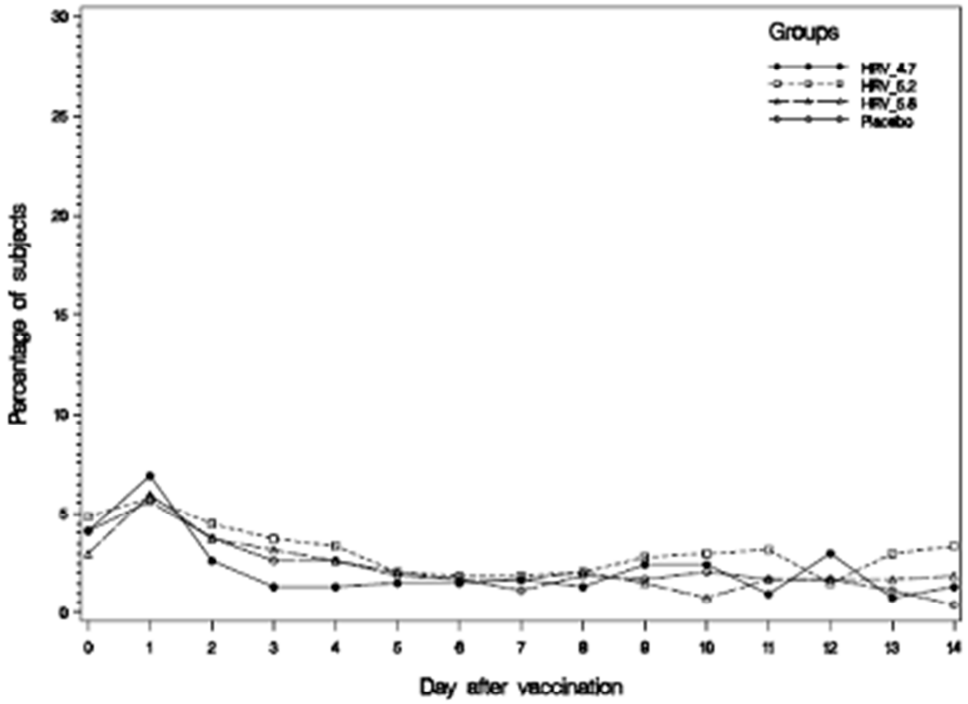


Figure 8 Daily report for Solicited Adverse Events



GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase IIB, randomised, observer-blind, placebo-controlled, multi-centre study to evaluate the efficacy, safety, reactogenicity and immunogenicity of the GSK Biologicals' investigational vaccine GSK3277511A when administered intramuscularly according to a 0, 2 months schedule in COPD patients aged 40 to 80 years with a previous history of acute exacerbation (AECOPD).
eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002) An observer-blind study to evaluate the efficacy, safety, reactogenicity and immunogenicity of the GSK Biologicals' investigational vaccine GSK3277511A when administered to COPD patients
Scope:	All analyses for the final clinical study report
Date of Statistical Analysis Plan	Final Version: 26-Oct-2017
Co-ordinating author:	PPD (Lead Statistician)
Reviewed by:	PPD (Clinical Research & Development Lead) PPD (Director Clinical Statistics) PPD (Peer Reviewer Statistician) PPD (Lead Statistical Analyst) PPD (Scientific Writer) PPD (Regulatory Affair) PPD (SERM Physician) PPD (Public disclosure representative) PPD (Vaccine Developer Leader) PPD (Clinical read-out team Leader)
Approved by:	PPD (Clinical and Epidemiological Project Leader) PPD (Director Clinical Statistics) 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
AECOPD	Acute exacerbation of Chronic Obstructive Pulmonary Disease
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATP	According to Protocol
CI	Confidence Interval
BMI	Body Mass Index
CMI	Cell-mediated immunogenicity
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CSR	Clinical Study Report
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
EXACT-PRO	EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
HCU	Healthcare utilisation
HRQOL	Health-related quality of life
ICS	Intracellular cytokine staining
iSRC	Internal Safety Review Committee
LL	Lower Limit of the confidence interval
Max	Maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MCAR	Missing Completed at Random
Min	Minimum value

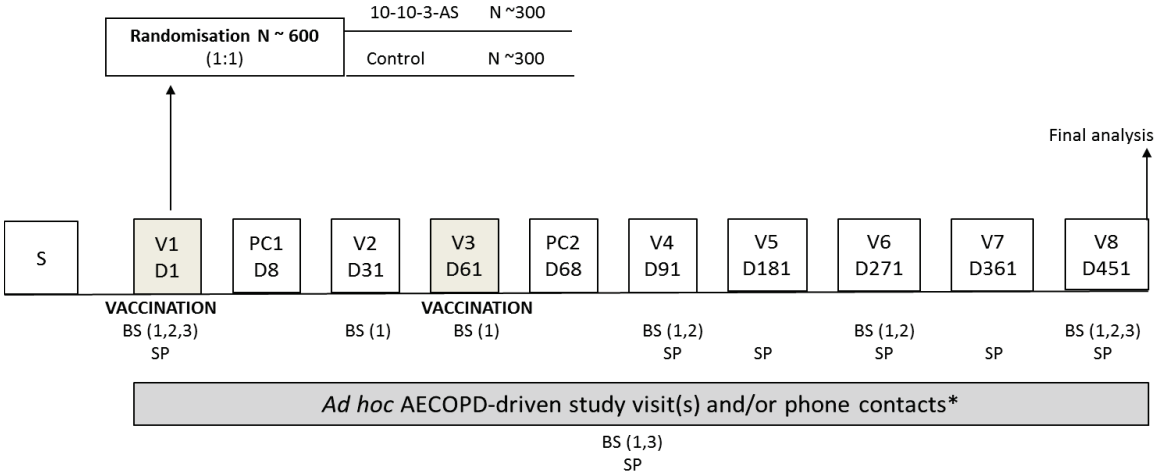
mTVC	modified Total vaccinated cohort
PCR	Polymerase chain reaction
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SERM	Safety Evaluation & Risk Management
SOC	System Organ Class
SRT	Safety review team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated cohort
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
23-OCT-2017	Final version	Final Version 2: 07 June 2017

2. STUDY DESIGN

Figure 1 Study design overview



S = Screening Visit; **V** = Visit; **PC** = Phone contact; **D** = Day; **FU** = Follow-up; **BS (1)** = blood sample for humoral immunogenicity; **BS (2)** = blood sample for cell-mediated immunogenicity (CMI), this blood sample will only be collected from a sub-cohort of subjects; **BS (3)** blood sample for biomarkers; **SP** = sputum sample
The allowed interval between Screening Visit and Visit 1 is 28 days. If a delay occurs for an eligible subject so that the interval exceeds 28 days, the entire Screening Visit needs to be repeated.
* An AECOPD visit should be scheduled as soon as possible after the onset of AECOPD symptoms (max 96 hours after and, if applicable, preferably before starting treatment with antibiotics).During this visit blood and sputum samples will be collected. In addition, follow-up phone call(s) and/or visit(s) will take place to determine the end of the AECOPD. These contacts will take place at least every 2 weeks until the AECOPD is resolved.

Investigational vaccine and placebo will be administered in addition to standard of care.

- **Experimental design**: Phase IIB, randomised, observer-blind, placebo-controlled, multi-centric study with two parallel groups.
- **Duration of the study:** for each subject enrolled, the study will last approximately 15 months from Visit 1 up to study completion (Visit 8).
  - Epoch 001: Screening Visit (Day -28 to Day -1).
  - Epoch 002 : Primary starting at Visit 1 (Day 1) and ending at Visit 8 (Day 451).
- **Primary completion Date (PCD):** Last Subject Last Visit (LSLV) from Visit 8 (Day 451) or last visit/contact of Epoch 002.

- **Study groups:**
  - **10-10-3-AS**: Approximately 300 subjects receiving two 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.
  - **CONTROL**: Approximately 300 subjects receiving two doses of placebo (PBS).

The following group names will be used for the statistical analysis

Table 1 Study groups and epochs foreseen in the study

Group order in tables	Number of subjects	Group label in tables	Group definition for footnote
1	~300	10-10-3-AS	2 doses of AS01E-adjuvanted NTHI/Mcat vaccine containing 10 mcg of PD, PE-PilA and 3 mcg of UspA2
2	~300	PLACEBO	2 doses of phosphate buffered solution

- **Sampling schedule:**
  - **Blood samples for assessment of humoral immunogenicity** will be collected from all subjects at Visit 1 (Day 1), Visit 2 (Day 31), Visit 3 (Day 61), Visit 4 (Day 91), Visit 6 (Day 271), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
  - **Blood samples for assessment of cell-mediated immunogenicity (CMI)** will be collected from all subjects in the CMI sub-cohort (approximately 60 subjects in each group) at Visit 1 (Day 1), Visit 4 (Day 91), Visit 6 (Day 271) and at Visit 8 (Day 451).
  - **Blood samples for biomarkers** will be collected from all subjects at Visit 1 (Day 1), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
  - **Blood sample for haematology profile** will only be collected at Visit 1.
  - **Sputum samples for PCR** (all subjects) **and culture** (50% of subjects) will be collected from all subjects at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 271), Visit 7 (Day 361), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
- **Other assessments:**

  COPD symptoms: All subjects will be asked to record COPD symptoms in their electronic Diary Card:
  - Daily in the morning throughout the study (including during AECOPD): **morning symptoms**.
  - Daily in the evening throughout the study (including during AECOPD): **EXACT-PRO**.

HRQOL assessments:

- All subjects will be asked to complete the COPD assessment test (CAT) at the Screening Visit (pre-Day 1), Visit 6 (Day 271), Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.
- All subjects will be asked to complete St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) at the Screening Visit (pre-Day 1), Visit 6 (Day 271), at Visit 8 (Day 451) and at each AECOPD visit from first vaccination to study conclusion.

Pre- and post-bronchodilator spirometry assessments will be done for all subjects at the Screening Visit (pre-Day 1), Visit 6 (Day 271) and at Visit 8 (Day 451).

3. OBJECTIVES

3.1. Primary objective

- To assess efficacy of the investigational vaccine as compared to the placebo control with respect to the rate of moderate and severe AECOPDs.

3.2. Secondary objectives

- To describe the safety and reactogenicity of the investigational vaccine.
- To assess efficacy of the investigational vaccine as compared to the placebo control with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe).
- To assess efficacy of the investigational vaccine as compared to placebo with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe) associated with NTHi and/or Mcat detected by PCR.
- To evaluate the humoral immunogenicity of the investigational vaccine.
- To evaluate the cellular immunogenicity of the investigational vaccine.

3.3. Tertiary objectives

- To evaluate the effect of the investigational vaccine on the presence and load of NTHi and/or Mcat at stable visits and AECOPD by PCR.
- To evaluate the effect of the investigational vaccine on the presence and load of NTHi and/or Mcat at stable visits and AECOPD in a subset of sputum samples by culture.
- To explore the efficacy of the investigational vaccine as compared to placebo with respect to the rate of all AECOPDs and by severity (i.e. mild, moderate or severe) associated with NTHi and/or Mcat detected in a subset of sputum samples by culture.
- To explore the impact of the investigational vaccine on health-related quality of life (HRQOL).

- To explore the impact of the investigational vaccine on use of medication for COPD and Healthcare Resource Utilisation.
- To explore the impact of the investigational vaccine on lung function.
- To describe selected biomarkers in stable COPD and during AECOPD.
- To explore the T helper profile of the PD-, PE-, PilA-, UspA2-specific CD4+/ CD8+ T cell responses.
- To collect blood and sputum samples for assay development, for lung microbiome analysis, to explore the level of inflammation (into the lung) and/ or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.
- To explore the data for an immune correlate of protection.

4. ENDPOINTS

4.1. Primary endpoint

- Rate of moderate and severe AECOPD (any cause), occurring within a period starting 1 month post-Dose 2 and lasting for 1 year.

4.2. Secondary endpoints

Safety:

- Occurrence of each solicited local AE, during the 7-day follow-up period (Day 1 - Day 7) following each vaccination.
- Occurrence of each solicited general AE, during the 7-day follow-up period (Day 1 - Day 7) following each vaccination.
- Occurrence of any unsolicited AE, during the 30-day follow-up period (Day 1 - Day 30) following each vaccination.
- Occurrence of any pIMD from first vaccination up to study conclusion.
- Occurrence of any SAE from first vaccination up to study conclusion.

Efficacy: All AECOPD

- Yearly rate of all AECOPD (any cause, any severity) starting 1 month post-Dose 2, in vaccinated and control subjects.
  - Rate of moderate and severe AECOPD cases in vaccinated and control subjects, during 3, 6 and 9 months observation starting 1 month post-Dose 2.
  - Rate of all AECOPD cases in vaccinated and control subjects, during 3, 6, 9 and 12 months observation starting 1 month post-Dose 2.
  - Rate of all AECOPD cases in vaccinated and control subjects, during 3, 6, 9 and 12 months observation starting 1 month post-Dose 2, by severity.

- Time to first moderate or severe AECOPD.
- Time to first AECOPD of any severity.
- Time to first AECOPD, by severity.
- Duration of moderate and severe AECOPDs.
- Duration of AECOPDs of any severity.
- Duration of AECOPDs, by severity.

Efficacy: AECOPD associated to bacteriological pathogens (PCR)

- Rate of NTHi-associated and/ or Mcat-associated moderate and severe AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year.
- Rate of NTHi-associated and/ or Mcat-associated any severity AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year.
- Rate of NTHi-associated and/ or Mcat-associated AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year, by severity.
- Time to first moderate or severe NTHi-associated and/ or Mcat-associated AECOPD.
- Time to first NTHi-associated and/or Mcat-associated AECOPD of any severity.
- Time to first NTHi-associated and/or Mcat-associated AECOPD, by severity.
- Duration of moderate and severe NTHi-associated and Mcat-associated AECOPD.
- Duration of NTHi-associated and/or Mcat-associated AECOPDs of any severity.
- Duration of NTHi-associated and/or Mcat-associated AECOPD, by severity.

Immunogenicity and CMI:

- Anti-PD, anti-PE, anti-PilA and anti-UspA2 total IgG antibody concentrations as measured by ELISA at Day 1, Day 31, Day 61, Day 91, Day 271 and at Day 451, in all subjects.

  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 271 and at Day 451, in a sub-cohort of subjects.

4.3. Tertiary endpoints

Sputum sample PCR:

- Occurrence (presence and absence) and bacterial load measured by PCR of NTHi and/or Mcat in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD visit.

Sputum sample culture:

- Occurrence (presence and absence) and semi-quantitative bacterial load measured in a subset of sputum sample by culture of NTHi and/or Mcat in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD visit.
- Rate of NTHi-associated and Mcat-associated, moderate and severe AECOPD.
- Rate of NTHi-associated and Mcat-associated any severity AECOPD.
- Rate of NTHi-associated and Mcat-associated AECOPD, by severity.
- Time to first moderate or severe NTHi-associated and/or Mcat-associated AECOPD.
- Time to first any NTHi-associated and rate Mcat-associated AECOPD.
- Time to first NTHi-associated and rate Mcat-associated AECOPD, by severity.
- Duration of each moderate and severe NTHi-associated and Mcat-associated AECOPD.
- Duration of NTHi-associated and/or Mcat-associated AECOPDs of any severity.
- Duration of NTHi-associated and/or Mcat-associated AECOPD, by severity.

QOL:

- Assessment of EXACT-PRO score, daily in the evening throughout the study, in all subjects.
- Assessment of CAT scores at Screening, Day 271 and Day 451, and from first vaccination to study conclusion for each AECOPD visit, in all subjects.
- Assessment of SGRQ-C score at Screening, Day 271 and Day 451, and from first vaccination to study conclusion for each AECOPD visit, in all subjects.
- Assessment of use of medication to treat (AE)COPD and healthcare utilization in all subjects throughout the study period.

Lung function:

- Assessment of FEV1% of predicted normal value at Screening, Day 271 and Day 451, in all subjects.

Biomarkers:

- Concentration of selected biomarkers (fibrinogen, hsCRP and IP-10), at Day 1 and Day 451, and for each AECOPD visit from first vaccination to study conclusion.

CMI:

- 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 271 and Day 451

Assay development, microbiome analysis and lung inflammation:

- Presence of respiratory viral pathogens in sputum (including respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) at Day 1, Day 91, Day 181, Day 271, Day 361, Day 451 and at each AECOPD visit from first vaccination to study conclusion
- Presence and/or concentration of inflammatory cytokines in sputum at Day 1, Day 91, Day 181, Day 271, Day 361, Day 451 and at each AECOPD visit from first vaccination to study conclusion on a subset of samples

5. ANALYSIS SETS

5.1. Definition

All enrolled set: All subjects who will sign the inform consent and for whom a subject code is assigned

The following study cohorts will be evaluated.

5.1.1. Total vaccinated cohort

The total vaccinated cohort (TVC) will include all subjects with at least 1 documented study vaccine administration:

- A **safety** analysis based on the TVC/ES will include all subjects with at least one vaccine dose administered and who provided safety data.
- An **immunogenicity/CMI/efficacy** analysis based on the TVC will include all vaccinated subjects for whom immunogenicity/CMI/efficacy data are available.

Note that in subjects receiving only one dose the efficacy endpoint is the number of moderate or severe AECOPD (any cause), occurring during 12 months observation period.

The TVC analysis will be performed per treatment actually administered at Dose 1.

5.1.2. Modified total vaccinated cohort

The modified total vaccinated cohort (mTVC) will include all subjects with 2 documented study vaccine administrations with respect to the vaccine actually administered.

The primary efficacy analysis will be performed on the mTVC.

5.1.3. According to protocol cohort for analysis of efficacy

The according-to-protocol (ATP – also called per-protocol) cohort for analysis of efficacy will include all subjects in the TVC:

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule.
- Who received the study vaccine according to protocol procedures.
- Who did not receive a medication/ product/ vaccine that may have an impact on the efficacy or bacteriological load.

  In addition for the Bacteriological efficacy endpoints:

- For whom the sputum sample results are available.

5.1.4. According to protocol cohort for analysis of immunogenicity and CMI

The ATP cohort for immunogenicity/CMI will include all subjects in the TVC:

Who met all eligibility criteria.

- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule.
- Who received the study vaccines according to protocol procedures.
- Who did not receive a concomitant medication/ product leading to elimination from the ATP (per-protocol) analysis for immunogenicity/CMI
- Who did not present an intercurrent medical condition leading to elimination from the ATP analysis for immunogenicity/CMI.
- Who complied with the blood sample timings.
- For whom post-vaccination immunogenicity results are available.

Note 1 that each of the above reasons for exclusion will be evaluated for each strain and each time point and thus different strains and time points could present different numbers of observations (N).

Note 2 that in order to align to ICH and CDISC terminology in the remaining part of this document the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively.

The modified Total Vaccinated Cohort (mTCV) will not be renamed.

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 (ES)

Code 100 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES (previous called TVC)

Code 1030.2 (2^{nd} dose of vaccine not administered at all) will be used to identify subjects eliminated by mTVC.

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

5.2.2.1. Excluded subjects

A subject will be excluded from the PPS (previously called ATP) analysis under the following conditions

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine not administered at all
1030.2	2nd dose of 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)
2040	Administration of any medication forbidden by the protocol
2080	Subjects did not comply with vaccination schedule
2090.a	Subjects did not comply with blood sample schedule
2090.b	Subjects did not comply with sputum sample schedule
2100.a	Serological results not available post-vaccination
2100.b	Sputum results not available post-vaccination
2100.c	CMI results not available post-vaccination for those in CMI subset
2100.d	Blood Biomarker results not available post-vaccination
2120	Obvious incoherence or abnormality or error in data

5.2.2.2. 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
1060.x+	Unblinding of subjects
1070.x+	Subjects got vaccinated with the correct vaccine but containing a lower volume
2040.x+	Subjects receive a vaccination/medication forbidden by the protocol

5.2.2.3. Visit-specific censored Data

Data from visit x will be censored 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
2090.x	Subjects did not comply with blood/sputum sample schedule at visit x
2100.a.x	Serological results not available for blood sample at visit x
2100.b.x	Bacteriological results not available for sputum sample at visit x

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

The following important protocol deviations, which will not lead to elimination from analysis, will be reported by groups:

- Manual randomization: In case of the randomization system is unavailable, the investigator has the option to call help desk and to perform a 'manual' randomization, which will be documented accordingly.
- In case unexpected vaccinations at study start were granted due to regulatory recommendation, the subjects who had such vaccination could be mentioned.
- Subjects for whom the spirometry could not be performed.
- Subjects without chest X-ray available
- Subjects of childbearing potential without pregnancy test for whom the pregnancy did not happen.
- Possible violation from lab manual having no impact on sputum or blood results
- Subject outside of AECOPD Visit windows

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 and baseline characteristics: age (in years), gender, ethnicity, smoking status at enrolment (i.e., screening visit) will be summarised by group using descriptive statistics.

Other variables GOLD grade at baseline, history of moderate and severe exacerbation in the last 12 months (<2 or ≥ 2, and total number), HRQOL baseline scores from CAT, SGRQ-C at enrolment visit (i.e., screening visit) will also be summarized as baseline characteristics.

- Frequency tables will be generated for categorical variable such as gender; geographical ancestry, age category, GOLD, smoking status and history of moderate and severe exacerbation;
- N, mean, median, standard deviation (SD) and min and max values will be provided for continuous data such as age, height, weight, body mass index (BMI), total number of exacerbation in previous 12 months and HRQOL baseline scores.

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

- Age in year (as continuous variable),
- Age category: 40-59 y, 60-80y
- Gender: Male, Female
- Race: (all reported in e-CRF)
- Ethnicity: Hispanic or Latino, Not Hispanic nor Latino
- Exacerbations in previous 12 months:
  - Total number
  - Mild
  - Moderate
  - Severe
- Exacerbations in previous 12 months category: <2, >=2
- Smoking status: yes, no
- Pack year (as continuous variable)

- GOLD grade category: 1 mild, 2 moderate, 3 severe, 4 very severe
- FE1/FVC category: >=70, <70
- CMI sub-cohort: yes, no
- Culture cohort: yes, no

The following variables will be included in vital sign summary and listing:

- Height (cm)
- Weight (kg)
- Body temperature (continuous variable)
- Body temperature category < 37.5°C, ≥ 37.5°C
- Hear rate
- Respiratory rate
- Systolic Blood Pressure,
- Diastolic Blood Pressure,
- Chest x-ray result: yes, no
  - Infiltrate presence (%): unilateral, bilateral
  - Pleural effusion (%): right chest, left chest, bilateral

Demographic and baseline characteristics will be tabulated for the Exposed Set (TVC) and mTVC, and no inferential analyses of are planned.

The distribution of subjects enrolled among the study sites and country will be tabulated as a whole and per group.

Number and percentages of subjects in each study cohorts (All enrolled, TVC, mTVC, and PPS) will be summarized by 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 any cohort of analyses will be tabulated.

6.1.2. Additional considerations

Physical examination:

- As part of the baseline characteristics, variables collected during the physical examination such as height, weight, BMI, pulmonary function test baseline values (such as FEV_1/FVC, FEV_1 and FEV_1 % of predicted), body temperature, heart rate, respiratory rate, Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values will be summarized by the mean of descriptive statistics.

Body temperature will be also categorized as Fever YES (≥ 37.5°C (99.5°F)) or NO (< 37.5°C (99.5°F))

Haematology profile:

Haematology profile is defined at visit 1 only and the following parameters will be analysed form whole blood:

Whole blood	Leukocytes (White Blood Cells) Neutrophils Lymphocytes Eosinophils Basophils Monocytes Erythrocytes (Red Blood Cells) Hemoglobin Platelets

For each group and for each **haematology parameter** descriptive statistics such as: mean, median, standard deviation, minimum and maximum will be tabulated, together with the percentage of subjects having results below or above laboratory normal ranges.

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.
- Similarly the frequencies and percentage of subject who received influenza or pneumococcal vaccination in the previous 12 months before enrollment will be reported overall and by vaccine group

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccinations will be summarized overall and by vaccine group. Data will be tabulated for the Exposed Set.

6.2.2. Additional considerations

None.

6.3. Efficacy/Effectiveness

Efficacy of the vaccine will be evaluated as both primary and secondary endpoint.

In the primary endpoint analysis, the 'clinical' vaccine efficacy is defined as reduction in 12 months rate of moderate and severe AECOPD (any cause) from one month after complete vaccine exposure.

In secondary endpoints a broader definition for efficacy is being investigated and the following rates are considered:

- Reduction in 3, 6, and 9 months rate of moderate and severe of AECOPD (any cause) starting from one month after complete vaccine exposure.
- Reduction in yearly rate of any grading of AECOPD (any cause) starting from one month after complete vaccine.
- Reduction in severity of AECOPD (any cause) starting from one month after complete vaccine.
- Reduction in yearly rate of moderate and severe of AECOPD associated with NTHi or Mcat, starting from one month after complete vaccine.
- Reduction in yearly rate of any grading of AECOPD associated with NTHi or Mcat, starting from one month after complete vaccine.
- Reduction in 3, 6, and 9 months rate of moderate and severe AECOPD associated with NTHi or Mcat starting from one month after complete vaccine exposure.
- Reduction in severity of AECOPD associated with NTHi or Mcat starting from one month after complete vaccine.

6.3.1. Analysis of efficacy planned in the protocol

The efficacy analysis will be performed on the mTVC and repeated on the ES. The efficacy analysis will also be repeated on the PPS if the percentage of vaccinated subjects excluded from the PPS for efficacy is more than 5%.

In the TVC cohort, if a subject receives only one dose the efficacy endpoint is defined as the number of (moderate or severe) AECOPD (any cause), occurring within a period starting from Day 90 and lasting for 1 year (i.e., until study conclusion).

Vaccine efficacy (VE) is expected to start at one month post-Dose 2 (Day 90), so the study period is divided in to two: from enrolment (Day 1 - day of first injection) up to one month post Dose 2 (Day 90) and from one month post Dose 2 (Day 90) until study end (Day 451).

Evaluation of VE and incidence rate of AECOPD in both study groups, together with CIs will be computed for each study periods.

6.3.1.1. Efficacy – Clinical Endpoints

6.3.1.1.1. Primary Analyses

The primary analysis method of the vaccine VE will consider the exact inference on the risk ratio (R_{vacc} / R_{con}) based the total number of moderate and severe AECOPD observed in one year time of follow up.

VE is defined as: $VE = 1 - R_{vacc} / R_{con}$

being

- R_{vacc} = average yearly incidence rate of AECOPD events per subject in the group 10-10-3-AS.
- R_{con} = average yearly incidence rate of AECOPD events per subject in the placebo group.

Inferential statistic

Incidence rates and VE with 87% and 95% CIs will be tabulated for primary efficacy endpoint. P-value (to test H_0 = [VE=0]) will be tabulated for the primary endpoint.

The efficacy of vaccine in preventing moderate and severe AECOPD will be demonstrated if the lower limit of the two-sided 87% CI of VE is above 0.

The primary outcome will be analysed using the Negative Binomial regression model with number of AECOPD as dependent variable; treatment (vaccine or placebo), age group (40 - 59 yrs or 60 - 80 yrs), GOLD grade (2, 3 or 4) and history of moderate and severe exacerbations (<2 or ≥ 2) and country as independent variables, with logarithm as link function, and the logarithm of time for follow-up (in years) as an offset variable.

The following SAS code will be applied for primary analysis:

```
PROC GENMOD data=<dataset>;
 CLASS trt age gold hexac country;
 MODEL nb_exac = trt age gold hexac country
      / dist=NegBin LINK=log OFFSET=logfu alpha=0.13;
RUN;
```

Where
trt= treatment arm;
age= Age Group
nb_exac=number of exacerbation
gold= GOLD grade at enrolment;
hexac= History of moderate/severe exacerbation;
country=Subject Country
fu= follow up time in year;
logfu= log(fu);

Similarly the CIs of the incidence rate will be computed using the same model which accounts for repeated events and the following SAS code will be applied:

```
PROC GENMOD data=<dataset>;
BY trt;
CLASS trt age gold hexac country;
MODEL nb_exac = age gold hexac country
      / dist =NegBin LINK=LOG OFFSET=LOGFU alpha=0.05;
ODS OUTPUT ParameterEstimates=out_parm NObs=Nobs;
RUN;

DATA parm_est(keep= val rate rate_LL rate_UL);
 SET out_parm(WHERE=(Parameter='Intercept'));
 format rate rate_LL rate_UL 8.2;
      val= "Yearly Rate from Negative Binomial";
      rate=EXP(Estimate);
      rate_LL=EXP(LowerWaldCL);
      rate_UL=EXP(UpperWaldCL);
 RUN;
```

Note: If the model does not converge, the Poisson distribution will be used instead of the Negative Binomial.

The number of AECOPD occurring from enrolment up to 1 month post-Dose 2 will be used as 'baseline' value. No difference between vaccine and placebo is expected in this period.

Descriptive statistics

For each treatment group, the total number of subjects, total number of AECOPD, total exposure time (in days), and incidence exacerbation rate (per year and per each sub period considered) together with the frequency of number of AECOPD will be tabulated.

The following statistics will be reported for exacerbation rate in the two treatment groups: N, mean, SD, median, Q1, Q3, min and max.

Sensitivity analysis

Primary analysis will be presented in three study populations: mTVC, TVC and PPS. In addition, a sensitivity analysis will be carried out using permutation test. Subjects will be grouped in to homogenous strata (based on the covariates and using a clustering procedure or similar methods). Treatment group will be permutated within each stratum. Then the negative binomial regression model for the number of AECOPD will be applied, for each permutation performed, without covariates (only treatment).

6.3.1.1.2. Secondary Analyses

Incidence rate of AECOPD

The following incidence rates of AECOPD (any type) occurring from enrolment up to 1 month post-Dose 2 will be computed together with 87% and 95% CIs, and incidence rates together with VE in the prevention of AECOPD (any type) will be computed over a period starting 1 month post-Dose 2 and lasting for 1 year, with 87% and 95% CIs:

- Any severity of AECOPD.
- AECOPD, by event severity.

Time to first AECOPD event

The time to first AECOPD events following complete schedule vaccination (i.e., 1 months post-Dose 2) will be analysed using Cox's proportional hazard regression model which include, with treatment, GOLD grade at enrolment (2, 3 or 4) and history of exacerbations (<2 or ≥ 2) as factors. Wald test and CIs will be produced.

The time to first event will be computed for the following:

- Time to first moderate and severe AECOPD
- Time to first any severity AECOPD.
- Time to first AECOPD, by event severity.

Hazard rate and CI will be derived using the following SAS code:

```
PROC PHREG data=<dataset>;
CLASS trt age gold hexac;
MODEL survtime*status(0)=trt age gold hexac / TIES=EXACT RISKLIMITS;
RUN;
```

In addition the survival curves for each vaccine group will be calculated non-parametrically, and presented graphically using the Kaplan-Meier (i.e., Product-Limit) method, using the following code:

```
PROC LIFETEST data=<dataset> method =KM plot=(survival(atrisk) logsurv);
TIME survtime*Status(0);
STRATA trt;
RUN;
```

survtime represents variable containing AECOPD times.
status represents censoring variable (0=censored, 1=event).

Duration of AECOPD event

The length of each AECOPDs will be tabulated and presented via descriptive statistics (mean, SD, median, Q1, Q3, minimum and maximum), for each treatment and for the two periods (before 1 month post-Dose 2 and after 1 month post- Dose 2).

Tables will be produces considering the following:

- Duration of moderate and severe AECOPDs.
- Duration of AECOPDs of any severity.
- Duration of AECOPDs, by severity.

Stratification and additional analysis

Incidence rates of AECOPD and VE, together with 87% and 95% CIs, will be computed for all study period (starting from day 1 until study termination) and at 4, 7, 10 and 13 months post-Dose 2, using the same model as for the primary analysis.

Similarly for the time-to-event and duration of AECOPD data will be also presented for the entire study period starting from Day 1 up to study termination.

In addition descriptive statistics for the incidence rates will be presented by patient severity (GOLD grade: 2, 3, or 4), by Country (USA, Canada, France, Spain, Belgium, UK, Germany and Italy), by history of exacerbations (< 2 or ≥ 2) and by age group (40 - 59 yrs or 60 - 80 yrs).

6.3.1.2. Efficacy – Bacteriological Endpoint (PCR)

An AECOPD will be considered 'associated' to NTHi and/or Mcat if the sputum sample, collected during AECOPD visit, will reveal the presence of those bacteria.

We can assume that more than 99% of H. influenzae isolates in sputum (derived from lung) are non-typeable (NTHi) (Wilkinson et al, Thorax. 2017 Apr 21. thoraxjnl-2016-209023supplement) and thus the presence of Hi bacteria in sputum during exacerbation will be used to determine AECOPD associated to NTHi.

In case of no sputum sample at such visit, or no bacteriological presence (i.e., Hi or Mcat) the event will not be counted.

Bacteriological vaccine efficacy (VE_{bact}) is defined as reduction in number of NTHi and/or Mcat associated AECOPD in vaccinated subjects compared to placebo subjects:

$VE_{bact} = 1 - R_{vacc} / R_{con}$

where

- R_{vacc} = average yearly incidence rate of AECOPD events associated to NTHi and/or Mcat per subject in the group 10-10-3-AS.
- R_{con} = average yearly incidence rate of AECOPD events associated to NTHi and/or Mca per subject in the placebo group.

VE_{bact} in prevention of NTHi and/or Mcat associated AECOPD will be evaluated via PCR method in all subjects. The statistical analysis will be performed in a modified TVC (mTVC) population as first line and repeated in the PPS cohort if more than 5% of subjects are excluded.

The mTVC is defined as all subjects in the ES (i.e. in TVC) who provide sputum sample results.

The following incidence rate together and VE_{bact} over a period starting 1 month post-Dose 2 and lasting for 1 year and their 87% and 95% CIs will be computed:

- NTHi and/or Mcat-associated moderate and severe AECOPD.
- NTHi and/or Mcat-associated all-severity AECOPD.
- NTHi and/or Mcat-associated AECOPD, by severity.
- The time until first moderate and severe NTHI and/or Mcat- associated AECOPD.
- The time until first NTHI and/or Mcat- associated AECOPD (any severity).
- The time until first NTHI and/or Mcat- associated AECOPD by severity.

In addition incidence rates of AECOPD associated to NTHi and/or Mcat, and VE_{bact} , together with 87% and 95% CIs will be evaluated for all study period starting from Day 1 until study completion and counting the AECOPD at 4, 7, 10 and 13 months post-Dose 2.

Inferential statistic

Number and proportion of sputum samples (obtained at each scheduled visits and at each AECOPD visits) positive for bacterial pathogens (Hi and/or Mcat) will be computed together with exact 95% CIs by group and overall. The exact CIs will be estimated assuming independence of bacterial results across sputum samples.

The bacteriological vaccine efficacy outcome will be evaluated using same model as for clinical efficacy with the following SAS code:

```
PROC GENMOD data=<dataset>;
 CLASS trt age gold hexac country;
 MODEL nb__bact_exac = trt age gold hexac country
      / dist=NegBin LINK=log OFFSET=logfu;
RUN;
```

Where
nb_bact_exac are AECOPD associated to NTHi and/or Mcat by PCR method

As for the primary endpoint the number of bacterial associated AECOPD occurring from enrolment up to 1 month post-Dose 2 will be used as ‘baseline’ value. No difference between vaccine and placebo is expected in this period.

Descriptive statistics

For each treatment group, the total number of subjects, total number of AECOPD associated to NTHi and/or Mcat, total exposure time (in days), incidence of bacteriological associated exacerbation rate (per year and per each sub period considered) and the frequency of number of AECOPD will be tabulated.

The following statistics will be reported for AECOPD associated to NTHi and /or Mcat: N, mean, SD, median, Q1, Q3, min and max.

6.3.1.3. Efficacy – Bacteriological Endpoint (culture)

Same set of analyses, as in the PCR efficacy bacteriological endpoint, will be performed in the subset of subjects for whom the culture sputum (collected at AECOPD visits) is performed

Approximately 50% of the subjects will be allocated to sputum culture analysis (depending on which site the subject belongs as not all sites are qualified and selected for culture analysis).

The selection of sites that will perform the sputum culture is based on site characteristics (i.e., presence of qualified laboratory) and only subjects enrolled in these sites will be considered for this analysis.

The analysis will be performed in the culture-subset of the modified TVC (mTVC) population. The mTVC is defined as all subjects in ES and in the subset for culture sample who provide valid culture sputum sample results.

6.3.2. Additional considerations

The number of AECOPD occurring during the 1 year follow-up period starting 1 month post-Dose 2 will be used to describe vaccine efficacy (VE). Exacerbation rate reported during this period will be calculated for each subject.

Only for the purpose of reporting summary statistics, the number of exacerbations during the 1-year follow-up will be imputed for subjects withdrawing from the study to provide an estimate of the number of exacerbations over the follow-up period. This calculation will only be performed for the descriptive statistics for the rate of exacerbations during 1 year follow up period since the modelling of exacerbations takes into account the number of exacerbations and the time of follow-up for each subject [see Annex 1].

Incidence rate of AECOPD will be also computed in sub period starting from 1 month post-Dose 1 up to 3, 6 and 9 months, and stating from Day 1 up to entire study duration (i.e., 1 year and 3 months).

Control of type I error

Inferential analyses for efficacy are planned to be performed at alpha level of 0.13 (two sided). No alpha adjustment for multiple testing in the secondary endpoints will be performed, nevertheless efficacy analysis, both primary and secondary endpoints will be also complemented with the 95% CI.

6.4. Immunogenicity and Cell-mediated Immunity (CMI)

6.4.1. Analysis of immunogenicity planned in the protocol

As first line, the immunogenicity analysis will be based on the PPS (ATP). If the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is more than 10%, a second line immunogenicity analysis will be performed on the TVC.

Within group assessment

For each group (i.e., vaccine and placebo), at each timepoint during which blood samples are collected for humoral immune response (i.e., Day 1, Day 31, Day 61, Day 91, Day 271 and at Day 451), and for each vaccine strain (i.e., PD, PE, PilA and UspA2), the following will be computed:

- Seropositivity rate and the associated exact 95% CI
- GMCs and the associated 95% CI

Seropositivity rate is defined a percentage (proportion) of seropositive subjects. Seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value, as specified in Table 2

Descriptive statistics

The $\log_{10}$ ELISA concentration and fold increase over pre-exposure (i.e., Day 1) will be tabulated via descriptive statistics such as N, mean, SD, median, min, max and 95% CI for each group, study visit (where immune blood draw is performed) and vaccine strain.

Similarly the proportion of seropositivity subjects will be tabulated together with N, number of seropositive subjects and percentage for each group, study visit and vaccine strain.

In addition the distribution of antibody concentrations for each strain will be displayed using Reverse Cumulative Distribution Curves (RCDF).

The percentages of subjects with positive (see Table 2) ELISA values (on log10 scale) will be plotted via RCDF, having the individual concentration on the X-axis and the percentage of subject with equal to or greater than the value on the Y-axis by strain and visit.

Between groups assessment

The between groups immunogenicity analysis will be carried out with an alpha =0.05, however these are descriptive comparisons with the aim to characterize the difference between groups and should be interpreted with caution considering that there will be no alpha adjustment for multiplicity.

GMCs and GMCs ratio

The difference between vaccine and placebo will be evaluated in terms of GMCs ratio (Vaccine/Placebo) and it will be tabulated for each time together with the 95% CIs of the GMC ratio between groups by using an ANCOVA model on the logarithm base10 transformation of the concentrations. This model will include the group (vaccine or control), age category (40 - 59 years or 60 - 80 years), GOLD grade (GOLD 2, GOLD 3 or GOLD 4) and country as fixed effects and pre-Dose 1 concentration (as covariate).

For each vaccine group and time point (Visit), adjusted GMCs, GMC ratios and their 95% CIs will be obtained by exponentiating (base 10) the least square means and the

lower and upper limits of the 95% CIs of the log10-transformed concentrations. These will be obtained from an ANCOVA with vaccine group, age category, GOLD grade, country and pre-Dose 1 concentrations, as implemented in the following SAS code:

```
PROC GLM data=<dataset>;
BY visit;
class trt age gold country;
MODEL log(titer) = trt age gold country log(prettier);
LSMEAN trt / CL PDIFF ALPHA=0.05;
RUN;
```

Seropositivity: proportion and difference between proportions.

The vaccine group difference will be also evaluated in terms seropositivity proportion difference calculated using a binomial distribution. For constructing the 2-sided 95% CIs for the difference between groups the usual normal approximation is not considered to be appropriate because these proportions could be close to 1. Therefore, the associated confidence interval for the differences in percentage will be constructed using the MN method (Miettinen O, 1985). In analyzing differences in proportions, the MN method assumes normality of the test statistic (or a chi-square distribution for the squared version) under the null hypothesis and the difference with the usual method is in the variance estimation. This method is implemented in SAS with the following code:

```
PROC FREQ data= <dataset>;
TABLES trt*count / RISKDIFF(CL=MN) ALPHA=0.05 ;
WEIGHT frequency / zero;
RUN;
```

Table 2 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit*	Cut-off*	Laboratory
SERUM	anti-PD antibody	ELISA	In house	EU/ml	153	GSK Biologicals** or GSK designated laboratory
	anti-PE antibody				8	
	anti-PilA antibody				7	
	anti-UspA2 IgG antibody				18	

EU/ml = ELISA unit per millilitre
* 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.

6.4.2. Analysis of CMI planned in the protocol

CMI analysis will be descriptive only and it will be performed in a subset of approximately 120 subjects for whom the CMI blood samples are collected (*see protocol* section 5.1 Number of subjects).

CMI analysis will be based on the PPS (ATP). If more than 10% will be excluded from the PPS for CMI, a second line CMI analysis will be performed on the CMI subset of the

TVC (i.e., All subjects with at least 1 documented study vaccine administration and for whom CMI data are available).

NTHi and Mcat- specific CMI responses as measured by flow cytometry ICS

Descriptive statistics

For each vaccine strain (PD, PE, PilA and UspA2) the frequency of specific $CD4^+$/ $CD8^+$ T-cells producing two or more markers (see Table 3) will be summarised by means of descriptive statistics (mean, SD, minimum, Q1, median, Q3, and maximum) for each group, and at each time point during which blood samples are collected for CMI subset (Day 1, Day 91, Day 271 and Day 451).

The frequency of CD4+ /CD8+ T-cells producing two or more markers upon in vitro stimulation with the antigen (induction condition) is presented per million of CD4+ T (CD8+ T) cells for the analysis and in percentage for the graphical representation (via BOX-plot).

The Geometric Mean (GM) frequency at each CMI timepoint (Day 1, Day 91, Day 271 and Day 451) and for each stimulation (vaccine strain) will be also computed by taking the anti-log of the mean of the log frequency transformations.

Table 3 Intracellular cytokines staining (Markers)

Method	Unit	Cytokine	Cytokine Label
Flow cytometry ICS	Number of specific CD4+/CD8+ T-cells /10^6	CD40L	CD40 Ligand
		IL-2	interleukin 2
		IL-13	interleukin 13
		IL-17	interleukin 17
		IFN-γ	interferon gamma
		TNF-α	tumour necrosis factor alpha

T helper profile

T helper profile of the specific CD4+ and CD8+ T cells response will be evaluated with the frequencies of strain (stimulation) specific $CD4^+$/ $CD8^+$ T-cells expressing each cytokine and will be summarised by means of descriptive statistics (mean, SD, minimum, Q1, median, Q3, and maximum) for each group and at time point: Day 1, Day 91, Day 271 and Day 451 and via BOX plot.

6.4.3. Additional considerations

Humoral immune response

Missing immunogenicity data are considered missing completed at random (MCAR) and therefore will not contain information that impact the results of the analysis (i.e., not informative). Imputation methods will therefore not be used.

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.

Cell-mediated immune response

The frequency of CD4+ or CD8+ T-cells expressing a marker (see Table 3) is presented per million of cells for the analysis and per hundred cells for the graphical representation.

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, 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).

$$\boldsymbol{Freq}^{\mathbf{2+}}_{\boldsymbol{Induction}} = \frac{\boldsymbol{n}^{\mathbf{2+}}_{\boldsymbol{Induction}} - \boldsymbol{n}^{\mathbf{2+}}_{\boldsymbol{background}}}{\mathbf{1000000}} \quad \boldsymbol{Log_e}\left(\boldsymbol{Freq}^{\mathbf{2+}}_{\boldsymbol{Induction}}\right) = \boldsymbol{Log_e}\left(\frac{\boldsymbol{n}^{\mathbf{2+}}_{\boldsymbol{Induction}} - \boldsymbol{n}^{\mathbf{2+}}_{\boldsymbol{background}}}{\mathbf{1000000}}\right)$$

$n^{2+}_{Induction}$ = Number of antigen-specific CD4+/CD8+ T-cells expressing two or more cytokines.

Each data will be obtained by subtracting the summary of the background value to each summary value. Values less than or equal to zero will be set to 1 for the purpose of geometric mean calculation and graphical representation.

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The safety analysis will be based on the ES (also called TVC).

All analyses will be based on the ‘as treated’ analysis set.

Safety analysis will be descriptive, no inference and formal statistical comparison is planned for the safety data.

Safety reporting period differs depending on safety endpoints. Table 4 shows the overview of the safety reporting

Table 4 Reporting periods for collecting safety information

Event	Screening Visit*	Visit 1 Dose 1	6 d post Dose 1	29 d post Dose 1	Visit 3 Dose 2	6 d post Dose 2	29 d post Dose 2	6 m post Dose 2	Study Concl
Timepoint		Day 1	Day 7	Day 30	Day 61	Day 67	Day 90	Day 241	Day 451
Solicited local and general AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
SAEs									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									
pIMDs									
Intercurrent medical conditions									

* i.e. consent obtained.
The double-bordered lines indicate timings of vaccination.
AE = adverse event; **SAE** = Severe adverse event; **GSK** = GlaxoSmithKline; **pIMD** = potential immune mediated diseases

6.5.1.1. Solicited Local and General Adverse Events:

The following local AE will be solicited for 7 days after each vaccination:

Table 5 Solicited local adverse events:

Local AE	Grading	Collection period
Pain at injection site	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
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 Day 61-Day 67
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 diameter0	Day 1-Day 7 Day 61-Day 67

The percentage of subjects with at least one local solicited AE reported in diary card within 7 days after each dose (Day 1-Day 7) will be tabulated together with the exact 95% CI. Similarly the percentage of doses followed by at least one local solicited AE will be tabulated together with the exact 95% CIs within each group.

The same tabulation will be done for grade 3 solicited local AEs.

The following general AE will be solicited for 7 days after each vaccination:

Table 6 Solicited general adverse events:

General AE	Grading	Collection period
Headache	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Fatigue	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Myalgia	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Chills	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Fever	0 : < 37.5°C 1 : 37.5°C to 38.0°C 2 : 38.1°C to 39.0°C 3 : > 39.0°C	Day 1-Day 7 Day 61-Day 67

The percentage of subjects with at least one general solicited AE reported in diary card within 7 days after each dose (Day 1-Day 7) will be tabulated together with the exact 95% CI. Similarly the percentage of doses followed by at least one general solicited AE will be tabulated together with the exact 95% CIs within each group.

The exact 95% CIs will be calculated assuming independence between doses

The same tabulation will be done for grade 3 solicited general AEs.

The percentage of subjects reporting each individual local and general solicited AEs during the solicited follow-up period (i.e., day of vaccination and six subsequent days after each vaccination) by grading will be tabulated with exact 95% CI after each dose and overall by group. The percentage of doses followed by each individual solicited local and general AE will be tabulated overall by group with exact 95% CIs [Clopper CJ,1934]

The exact 95% CIs will be calculated assuming independence between doses.

For fever (irrespective of route of measurement), additional analyses will be performed 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

6.5.1.2. Unsolicited Adverse Events:

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 e-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 (SOC) and preferred term within SOC. 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.

The percentage of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) during a 30-day follow-up period after each dose (Day 1 –Day 30) will be tabulated with exact 95% CI for each

group. The same tabulation will be performed by severity, and for unsolicited AEs with a relationship to vaccination.

SAEs, death, pIMDs and AE leading to withdrawal reported during the entire study will be tabulated (from Day 1 until study termination) and listed.

In addition, SAEs related to study participation or concurrent GSK medication/vaccine reported from inform consent signed until entire study duration will be also listed.

This study foreseen two injections (i.e., two vaccinations) for each subject, and thus unsolicited AEs summary tables will be presented overall and by period of onset and will include frequency distributions of the different adverse events:

Number and percentage of subjects with the following AEs will be computed:

Onset between day 1 and Day 30 after each vaccination:

- Any AE after each vaccination (overall)
- Any AE after each vaccination, by vaccination
- By severity AE after each vaccination (overall)
- By AE severity after each vaccination, by vaccination
- Possibly or probably related unsolicited AEs after each vaccination (overall)
- Possibly or probably related unsolicited AEs after each vaccination by vaccination
- Possibly or probably related unsolicited AEs by severe after each vaccination (overall)
- Possibly or probably related unsolicited AEs by severe after each vaccination by vaccination
- Any medically attended unsolicited AE (overall).
- Any medically attended unsolicited AE, by vaccination

Onset between day 1 and Day 450 (study termination):

- Any serious adverse events (SAE) (overall).
- Any serious adverse events (SAE) by vaccination.
- Possibly or probably related SAE (overall).
- Any AE leading to death (overall).
- Any unsolicited AE leading to premature withdrawal from study (overall).
- Any potential immune mediated diseases (overall)
- Any potential immune mediated diseases by vaccination
- Any AE leading to hospitalization (overall).

Onset between Screening and Day 450 (study termination):

- Any SAE related to study participation or concurrent GSK medication or vaccine (overall).

6.5.2. Additional considerations

For solicited symptoms, missing or unevaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC (also called ES) will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

Solicited adverse events continuing beyond day 7 will be followed until resolution (up Day 30). Solicited AEs which will start after the day 1- day 7 after vaccination will be reported as unsolicited AE and coded by MedDRA as per Table 7.

For the unsolicited symptoms and concomitant medications/ products/ vaccinations, all vaccinated subjects will be considered and subjects who miss reporting symptoms/concomitant medications/ products/ vaccinations will be treated as subjects without unsolicited symptoms or concomitant medications/ products/ vaccinations, respectively.

6.5.2.1. Exclusion of implausible solicited Adverse Event

Some local and general 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 below:

Table 7 Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Redness	≥ 900 mm < 0 mm
Swelling	≥ 500 mm < 0 mm

6.5.2.2. 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:

Table 8 MedDra coding for solicited AE

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

The following results will be tabulated:

The percentage of subjects with at least one **local type AE** (solicited and unsolicited), with at least **one general** adverse event (solicited and unsolicited) and with **any AE** during the solicited follow-up period, i.e., the day of vaccination and six subsequent days after each vaccination will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be done for grade 3 AEs.

The percentage of doses followed by at least one **local AE** (solicited and unsolicited), by at least one **general AE** (solicited and unsolicited) and by **any type AE** will be tabulated, overall vaccination course, with exact 95% CI. The same tabulation will be done for grade 3 AEs.

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events is requested by System Organ Class and preferred terms and according to occurrence of each event. For this purpose the following additional analysis will be produced:

- The number of occurrence of the 5% most frequent non-serious unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination.
- The number of occurrence of SAE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination.

6.5.2.3. Pregnancies:

In case of any pregnancy from visit 1 (first vaccination) up to entire study duration, pregnancy reports and outcomes will be reported.

6.5.2.4. Clinical Safety Laboratory Investigations

Haematology profile, including differential cell counts is performed only a visit 1, before vaccination, and it will be summarized as baseline characteristics (see section 6.1.2) via descriptive statics. For each parameters: N, mean, median, SD, min and max will be computed and the frequencies of subjects with values above or higher normal ranges by treatment group.

6.5.2.5. Concomitant Medication

This analysis will consider all medications taken (and reported) for different purpose then COPD or AECOPD. The analysis of medications to treat COPD or AECOPD (standard of care and not standard of care) is described in section 6.6.2.

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects starting/reporting concomitant medications within the 7-day follow-up period (day 1 – day 7), during the 30-day follow-up period (day 1 – day 30) post-vaccination and during the entire study period will be tabulated by vaccine group for each study dose and across doses.

6.6. Other Analysis

6.6.1. Microbiological assessment

6.6.1.1. Sputum sample collection and quality

Sputum sample collection

Patient sputum sample will be collected (as stable visit) at Day 1 (before vaccination) and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD driven visit, where AECOPD is confirmed.

Within each vaccine group the percentage of patients at each study visit (stable visit) and AECOPD confirmed visit will be computed overall and by the method (i.e., spontaneous at study visit or spontaneous at patient's home, induced using 0.9% saline or induced using 3% saline).

The proportion of sputum samples obtained at each stable or AECOPD visit and positive for specific bacterial pathogens by bacteriological culture and PCR will be computed, by vaccine group.

Sputum sample quality

The quality of sputum is assessed via squamous cells count, neutrophils cells count and bacteria direct smear. These will be summarized at any sputum visit (stable) and at any AECOPD confirmed visit, via frequencies tables (i.e., frequencies of sputum samples per quality scores (see section 11.2.7) within each vaccine group)

If more than 10% of sputum samples have bad quality the analyses of bacteriological efficacy endpoint and bacteriological load (via PCR and culture) will be repeated in the subset of sputum samples with good and moderate quality.

6.6.1.2. Sputum bacterial/viral results via qPCR

Occurrence and load of Hi and/or Mcat

For each vaccine group the following analysis will be presented for sputum sample analysed via PCR:

- Overall proportion of sputum samples positive for Hi and Mcat with associated 95% CIs before vaccination (Day 1) and at any stable visit (Day 91, Day 181, Day 271, Day 361, Day 451) Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit
- Proportion of patients with sputum samples positive for Hi and Mcat with associated 95% confidence intervals (CIs), at each stable visit and at each AECOPD visit confirming acute exacerbation
- Summary statistics (N, mean, SD, median, minimum and maximum) and 95% CIs for the Hi and Mcat load will be displayed at each stable visit and at each AECOPD visit.

For the overall proportion, estimate and confidence intervals will be computed using a Generalized Estimating Equations (GEE) model assuming a binomial distribution for the response variable with logit as link function and a compound symmetry correlation matrix (exchangeable structure) to account for the within-patient correlations (Liang KY. 1986) and the following SAS code will be apply for stable visits, AECOPD visits separately and for Hi and Mcat bacteria:

```
PROC GENMOD data=<dataset> descending;
CLASS pid trt;
BY bacteria;
MODEL sp_positive = trt / dist = bin LINK = logit lrci ;
REPEATED subject=pid/ type=exch PRINTMLE;
ODS OUTPUT ParameterEstimates=out_parm ClassLevels=Class;
RUN;

DATA result;
 SET out_parm(where=(parameter='Intercept') drop=ChiSq ProbChiSq DF);
 format percent LL UL percent8.1;
      Percent=exp(estimate)/(1+exp(estimate));
      LL=exp(LowerLRCL)/(1+exp(LowerLRCL));
      UL=exp(UpperLRCL)/(1+exp(UpperLRCL));
      unit=_N_;
RUN;
```

where:

pid: patient id
trt= treatment arm;
sp_positive=sputum sample positive to bacteria (Hi or Mcat)

Other bacteriological pathogens

In addition to proportion of sputum positive to Hi (*Haemophilus influenza)* and Mcat (*Moraxella catarrhalis)* also the proportion of sputum samples obtained from PCR at pre-vaccination (Day 1), at Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit that are positive for specific bacteria (such as *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and *Streptococcus pyogenes* [*S. pyogenes*]) and virus (such as *respiratory* syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) will be presented together with the 95% CIs.

6.6.1.3. Sputum bacterial/viral results via culture

In the subset of subjects from whom the sputum will be analysed also by culture, the proportion of subjects with sputum sample positive and the number and proportion of sputum sample positive to Hi (with or without the *H.* influenzae confirmation by PCR of the collected bacterial isolates) and Mcat by culture will be displayed at each stable visit and at each AECOPD visit together with the 95% CIs, within each treatment group, using the same method as for PCR.

Frequencies of semi-quantitative bacteriological load (few scattered, +, ++, +++), for each vaccine group will be tabulated.

Other bacteriological pathogens

In addition to proportion of sputum positive to Hi (*H. influenza)* and Mcat (*M. catarrhalis)*, also the proportion of sputum samples at pre-vaccination (Day 1), at Day 91, Day 181, Day 271, Day 361, Day 451 and at any AECOPD visit that are positive to *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and other bacteria identified via culture, will be presented together with the 95% CIs.

6.6.2. Health related quality of life (QOL)

The following analysis are exploratory and a p-value <0.1 will be considered statistically significant, however 2-sided 95% CIs will be computed to show precision of estimation. All comparisons should be interpreted with caution considering that there will be no adjustment for multiplicity.

For each of the following questionnaire missing items will not be imputed and subjects with partial data will be excluded.

EXACT-PRO daily score

The EXAcerbations of Chronic pulmonary disease Tool (EXACT) constitutes of 14 items which are patient-reported outcome (PRO) via daily diary.

All EXACT-pro scores will be divided in to the following periods:

- Screening: scores collected between screening and Visit 1 (Baseline)
- Treatment: scores collected between Visit 1 and Visit 4 (i.e., 1 month post-Dose 2)

- Exacerbation: scores collected during the start date of an exacerbation until resolution.
- Follow –up: scores collected between Visit 4 (one month post-Dose 2) until study completion (one year after - Visit 8).
- Follow-up will be also divided by 3 months sub period:
  - from Visit 4 to Visit 5 (Day 91 to Day 180)
  - from Visit 5 to Visit 6 (Day 181 to Day 270)
  - from Visit 6 to Visit 7 (Day 271 to Day 360)
  - from Visit 7 to Visit 8 (Day 361 to Day 450)

Descriptive statistics

For each subject the average score across all days, within each period is computed. The mean score will be reports as descriptive statistics within each group (i.e., vaccine and placebo). N, mean, SD, median, min and max, on the **EXACT-PRO** average scores will be tabulated during all (stable) periods and during exacerbations.

Between groups comparison

At each period and sub period the two groups will be compared using an ANCOVA model, with the baseline value (i.e., score at screening) as covariate and treatment as fixed factor.

Note: EXACT-PRO baseline score at screening will be computed as the average within-patient score collected between screening Visit and Visit 1. If fewer than 4 days scores are available, the EXACT baseline score cannot be calculated and it will results as missing.

COPD Assessment Test (CAT)

COPD Assessment test (CAT) is a patient-completed questionnaire assessing globally the impact of COPD (cough, sputum, dyspnoea, chest tightness) on health status. It constitutes of 8 items each scoring from 1 to 5. The Total score is given by the sum of the single item scores and it ranges from 0 to 40. Higher scores denote a more severe impact of COPD on patient's life.

CAT questionnaire will be provided to all enrolled patients at Screening, Day 271 and Day 451 (end of study), and at each AECOPD visit.

Descriptive statistics

Descriptive statistics (N, mean, SD, median, Q1 and Q3, min and max) on the CAT total score (obtained as sum of the scores of 8 single items) will be reported by scheduled visits (stable visits), by AECOPD visit and by each treatment group.

Data will be also represented via line-chart for the total score at each time points (screening, Day 271, Day 415 and any AECOPD visit) together with the 95% confidence interval around the mean of the total score.

Within group change

For each group and at each time point (Screening, Day 271 and Day 421), the mean of total score together with SD will be reported and a pair t-test will be performed to compare screening scores with scores at Day 271 and at Day 421.

Between groups comparison

Differences between groups will be analysed in terms of difference in mean for each time points (Day 271 and Day 421) by one-way ANOVA model on the total scores, with vaccine group as factor.

CAT Score at AECOPD Visit

N, mean, SD, median, Q1 and Q3, min and max CAT score during AECOPD visit will be displayed according to the number and severity of AECOPD event.

St. George's Respiratory Questionnaire assessment (SGRQ-C)

The St. George's Respiratory Questionnaire (SGRQ) is composed of 76 items that are weighted to produce three component scores: Symptoms: measuring distress caused by respiratory symptoms, Activity: measuring the effect of difficulties in mobility and physical activity, and Impact: quantifying the psychosocial impact of the disease.

A "Total" score is also computed as sum from all component items score, thus providing a global estimation of the patients respiratory health. Each of these scores ranges from 0 to 100, a score of 100 indicating maximum disability (*Jones PW,1991*)

SGRQ-C will be provided to all enrolled patients at Screening, Day 271 and Day 451 (end of study), and at each exacerbation visit.

Descriptive statistics
Descriptive statistics (N, mean, SD, median, Q1, Q3, min and max) on the SGRQ-C (total score and symptoms, activity and impacts component scores) will be reported by scheduled visits (stable visits), at each AECOPD visit and by each treatment group.

Mean score for each component (symptoms, activity and impacts) and mean total scores will be also represented via line-chart at each time points (screening, Day 271, Day 415 and any AECOPD visit) together with the 95% confidence interval around the mean.

Within group change

For each group and at each time point (Screening, Day 271 and Day 421), the mean of each component score and the mean of total score together with SD will be reported and a pair t-test will be performed to compare screening scores with scores at Day 271 and at Day 421.

Between groups comparison

For all components and for the total scores, differences between groups will be analysed in terms of difference in mean for each time points (Day 271 and Day 421) by one-way ANOVA model on the total scores, with vaccine group as factor.

SGRQ-C at AECOPD Visit

N, mean, SD, median, min and max, of each component scores and of total score during AECOPD visit will be displayed according to the number and severity of AECOPD event.

Use of medication to treat (AE)COPD and Healthcare utilization (HCU)

Frequency table on the number and type of healthcare utilisation (Physician's office, Visit to Urgent Care, Visit to Emergency Department, Hospitalization) during entire study period will be presented overall and by vaccine group.

Same frequency table will be also presented for two sub-periods: all HCU before 1-month after second vaccination and all HCU between 1-month after second vaccination and study end.

Frequency table on the use of medication for COPD (or AECOPD) and type (Chronic use for COPD, Chronic use for other disorders, exacerbation rescue medication) during entire study period will be presented overall and by vaccine group.

Medications will be coded using the GSKDRUG dictionary and frequencies table by GSKDRUG code will be also reported for entire study period, overall and by vaccine group.

As for HCU frequency tables will be presented also for the two sub-periods: before 1-month after second vaccination and after 1-month after second (until study completion).

6.6.3. Lung function and biomarkers

Pre- and post-bronchodilator spirometry

Pre- and post-bronchodilator spirometry assessments will be done at the Screening Visit (pre Day 1), Visit 6 (Day 271) and at Visit 8 (Day 451).

The following pulmonary function parameters will be evaluated:

- Forced Expiratory Volume in 1 second (L): **FEV_1**
- Forced Expiratory Volume in 1 second percent of predicted (%): **FEV_1PP**
- Forced Vital Capacity (L): **FVC**
- Forced Vital Capacity percent of predicted (%): **FVCPP**
- FEV_1 and FVC ratio: **FEV_1/FVC**
- Peak Expiratory Flow (L/sec): **PEF**
- Forced expiratory flow between 25% and 75% of FVC (L/sec): **$FEF_{25-75\%}$**
- FEF between 25-75% of FVC percent of predicted(%): **$FEF_{25-75\%}$PP**

Descriptive analysis (N, mean, SD, median, min and max) on all spirometric measurements at each time point.

Biomarkers

The following selected biomarkers will be evaluated at Day 1 and Day 451 and at each AECOPD visit: fibrinogen, hsCRP and IP-10.

Descriptive statistics (N, mean, SD, median, min and max) will be tabulated for each biomarker and at each time point.

6.6.4. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate humoral immune responses to vaccination and efficacy (i.e., reduction in AECOPD). Details of the methodologies will be included in ad hoc SAP for this purpose.

7. ANALYSIS INTERPRETATION

The primary objective analysis (efficacy) of this study will be evaluated at alpha error of 13% (two-sided test) which is the measurement of the accuracy of our estimation.

Also 2-sided 95% CIs will be provided to show the precision of estimation.

For the secondary objectives we have the following:

- Inferential analyses for efficacy are planned to be performed at alpha level of 0.13 (two sided). No alpha adjustment for multiple testing in the secondary endpoints will be performed, nevertheless the 2-sided 95% CIs will be also provided
- All analyses for immunogenicity are planned to be performed at alpha level of 0.05 with no adjustment for multiplicity.

CMI and safety analyses are intended to be descriptively only.

All tertiary objectives are exploratory and a p-value <0.1 is considered as reference for statistical significance in comparative analysis. Those comparisons should be interpreted with caution.

8. CONDUCT OF ANALYSES

The analyses of the primary, secondary and tertiary endpoints will be completed once data are released. They will be finalized at the end of the trial, when all data up to and including Visit 8 (Day 451) will be available and cleaned.

An integrated clinical study report containing all data will be written and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These data will be documented in annex(es) to the study report and will be made available to the investigators at that time.

In addition to the data and analysis for the clinical study report, four safety interim data evaluations will be carried by an internal Safety Review Committee (iSRC).

8.1. Sequence of analyses

The following safety interim analyses performed by iSRC are planned:

First one will be done once 60 subjects complete one month after first vaccination (i.e., the first 60 subjects completed Visit 2-Day 31)

Second one will be done once 60 subjects complete one month after second vaccination (i.e., the first 60 subjects completed Visit 4- Day 91)

Third one will be done once 300 subjects complete one month after first vaccination (i.e., the first 300 subjects completed Visit 2- Day 31)

Fourth one will be done once 300 subjects complete one month after second vaccination (i.e., the first 300 subjects completed Visit 4- Day 91)

Table 9 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
60 subj safety post dose 1	E1_02	Internal	N	N	See SRT column in TOC
60 subj safety post dose 2	E1_03	Internal	N	N	See SRT column in TOC
300 subj safety post dose 1	E1_04	Internal	N	N	See SRT column in TOC
300 subj safety post dose 2	E1_05	Internal	N	N	See SRT column in TOC
All data analysis	E1_01	Study report	Y	Y	All tables in final TOC`

8.2. Statistical considerations for interim analyses

Four unblinded interim analyses to evaluate the safety during the exposure period will be conducted. These analyses will be performed from an internal board (iSRC) and no one in the study team will be part of the vaccine unblinded review of safety data.

The iSRC will conduct *unblinded* reviews of all available safety data from the present study while taking into account any other findings that could have an impact on the safety of the subjects, and will determine whether there is a safety signal that needs to be escalated to GSK Biologicals' VSMB. In the event that a safety signal is observed, GSK Biologicals' VSMB might decide to suspend, modify or continue the conduct of the study.

Before each iSRC safety evaluation in this study, the SRT will review the same safety data, but in a ***blinded*** manner.

In addition to the planned iSRC (and SRT) evaluations, *ad hoc* safety evaluations can take place if a safety concern is identified by an investigator or by the SRT.

Interim analysis unblinded data will not be circulated outside of the iSRC team and no individual clinical study report will be written as a result of these safety evaluations.

The planned interim analyses are only for safety monitoring. No conclusions on efficacy, immunogenicity or other endpoints will be carried out, thus no alpha adjustment will be performed.

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 analyses and their role (synopsis, in-text, post-text, 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.

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

Jones PW, Quirk FH, and Baveystock CM. "The St. George's Respiratory Questionnaire." *Respiratory Medicine* 1991. 85(Suppl. B):25-31.

Liang KY, and Zeger SL. "Longitudinal Data Analysis Using Generalized Linear Models." *Biometrika* 1986; 73:13-22

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

Newcombe RG, "interval estimation for the difference between independent proportions: comparison of eleven methods" *Statistics in Medicine* 1998; 17: 873-890

Stockley RA, Chopra N and Rice L. "Addition of salmeterol to existing treatment in patients with COPD: a 12 month study." *Thorax* 2006; 61:122-128

Wilkinson TMA, et al. A prospective observational cohort study of the dynamics of airway pathogens and the seasonal aetiology of exacerbations in chronic obstructive pulmonary disease" *Thorax 2017;0:1–9. doi:10.1136/thoraxjnl-2016-209023):*.

Handling missing efficacy data:

Efficacy – Clinical Endpoint

Missing or non-evaluable measurements will not be replaced. The only exception is for descriptive purposes in the primary objective tables and imputation is detailed below.

The number of exacerbations per year will be extrapolated for patients withdrawing from the study to provide an estimate of the number of exacerbations over the one year observation period. The number of exacerbations in a year will be calculated by multiplying the number of exacerbations experienced by the patient by 13 and dividing by the number of 4-week periods the patient was followed up [Stockley RA. 2006].

$$\text{Number of exacerbations per year} = \frac{\text{Number of exacerbations} * 13}{\text{Number of 4-week observation period intervals}}$$

The calculation of exacerbation rate will be based on follow-up period intervals of four weeks to avoid obtaining high imputed rates if a patient withdrew very early from the study after experiencing an exacerbation. Four-week intervals will be adopted since treatment courses for moderate/severe exacerbations are <=2 - 4 weeks when appropriate

Efficacy – Bacteriological Endpoint

For a given subject and a given bacteriological measurement, missing or unevaluable measurements will not be imputed.

Subjects who did not have any sputum collected or have missing measurements at all AECOPD (if at least 1 AECOPD occurred) will not be taken into account for the NTHi and/or Mcat-associated AECOPD analyses.

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI *[Clopper CJ. 1934]*.

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the paper from Robert G. Newcombe: interval estimation for the difference between independent proportions: comparison of eleven methods [Newcombe RG, 1998]. The standardised asymptotic method used is the method six.

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 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.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which injection occurred. More specifically dose 1 refers to all injections administered at the first vaccination visit (Visit 1) while dose 2 corresponds to all injections administered at the second vaccination visit (Visit 3) 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.
- The number of doses for a product is the number of time the product is 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 Kilogramm= weight in Pounds / 2.2

  – Weight in Kilogramm =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 (ie 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.

11.2.4. Efficacy

- **AECOPD events**: AECOPD events are confirmed according to investigator judgment after an AECOPD visit which is aimed to exclude worsening in symptoms not related to an AECOPD event.

eDiary alerts refer to daily symptoms recorded the morning after (also called morning symptoms). Alerts are based on the Anthonisen criteria:

- Worsening of two or more of the following major symptoms for at least two consecutive days*: dyspnea, sputum volume, sputum purulence (color)

  Or
- Worsening of any major symptom together with any of the following minor symptoms for at least two consecutive days*: sore throat, cold (nasal discharge and/or nasal congestion), fever (oral temperature $\geq$ 37.5°C) without other cause, increased cough, increased wheeze.

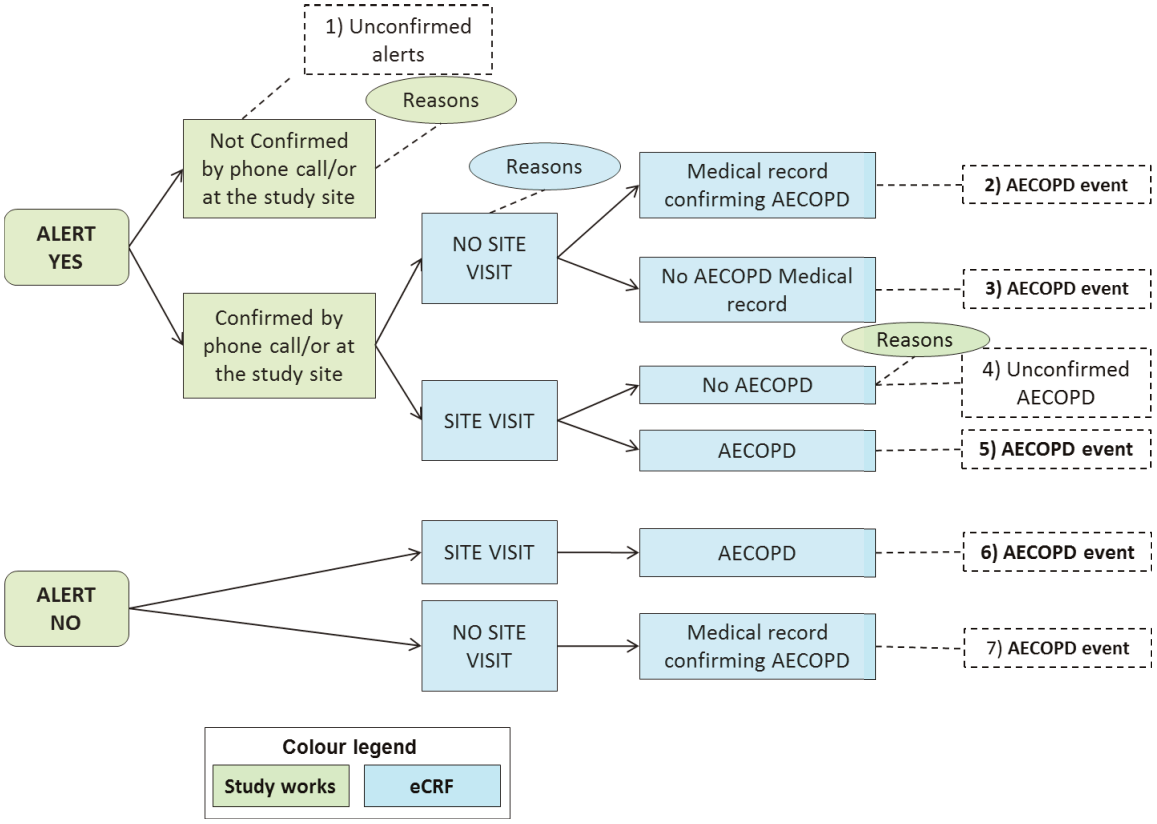
** The same two symptoms do not have to be present on both days as long as at least one major symptom is present on both days.*

AECOPD visits are scheduled after an electronic Diary Card alert confirmed by the investigator (by phone call or at the study site) or after spontaneous site visits due to worsening symptoms without any alert.

Potential AECOPD will be confirmed and registered as AECOPD event based on the following scheme:

- eDiary ALERT + phone call no confirmed = NO AECOPD event
- eDiary ALERT + phone call confirmed + site visit confirmed = AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no confirmed = NO AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no performed + Medical record confirmed = AECOPD event.
- eDiary ALERT + phone call confirmed + site visit no performed + Medical record no confirmed = NO AECOPD event.
- eDiary ALERT + phone call confirmed + site visit NO performed + Medical record no available = AECOPD event.
- eDiary NO ALERT + site visit NO confirmed = NO AECOPD event.
- eDiary NO ALERT + site visit confirmed = AECOPD event.
- eDiary NO ALERT + site visit NO performed + Medical record confirmed = AECOPD event.
- eDiary NO ALERT + site visit NO performed + Medical record no available/no confirmed = NO AECOPD event

Figure 2 AECOPD assessment



- **AECOPD onset date**: AECOPD onset will be defined as the first day of the two consecutive days of worsening symptoms.
- **AECOPD recovery date:** AECOPD recovery will be determined / confirmed by the investigator/delegate during (a) follow-up phone call(s) which will take place every 2 weeks until the AECOPD has resolved. The end date will be based on when the investigator/delegate determines that the AECOPD symptoms have resolved. In determining this end date, consideration will be given to symptoms recorded in the electronic Diary Card and patient assessment during the phone calls.
- **AECOPD duration** will be defined as the number of days from AECOPD onset (included) and AECOPD recovery (not included).

  Duration = date2 – date1,

  with date2: AECOPD recovery date,

  date1: AECOPD onset date
- **Unconfirmed AECOPD event with morning e-diary signal alert notification:** An alert from the electronic Diary Card not confirmed to be an AECOPD after contact by phone call or at the study site.

- **Grading of severity of an exacerbation:** Severity of exacerbations is defined as per protocol:
  - Mild: Worsening symptoms of COPD that are self-managed by the patient.
  - Moderate: Worsening symptoms of COPD that require treatment with oral corticosteroids and/or antibiotics.
  - Severe: Worsening symptoms of COPD that require treatment with in-patient hospitalisation or home care intervention.

Severity of the exacerbation will not be derived but taken directly from the information entered in the CRF (i.e. Severity of exacerbation will be taken from the conclusion of the exacerbation visit).

11.2.5. 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/Titres (GMC/Ts) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres 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 GMT calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol (see also Table 2).
- 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.
- 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.

11.2.6. 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 adverse events within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited adverse events based on the Total Vaccinated Cohort (TVC) 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.
- All solicited adverse events will be considered probably related to study vaccine.

Unsolicited adverse events: 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 adverse event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

- Unsolicited AE will be classified in the e-CRF as possibly related to study vaccine (YES or NO), based on the PI judgment.
- The related dose for an event (e.g., AE, medication, vaccination,…) is the study dose given before an event. In case the event takes place on a day a study dose is given, the related dose will be that of the study dose even if the event actually took place before. For instance, for a conc. medication started on the day of study dose 2 but before dose 2 administrations, the related dose will be dose 2.

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.

Table 10 Denominator for safety tables

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Solicited general adverse event	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 adverse event	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 adverse event	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
Concomitant vaccination	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.

Table 11 Number of decimals per parameter

Parameters	Number of decimal digits
% of count, including LL & UL of CI	1
p-value	3
Mean, median	Number of decimals in the raw data + 1
SD	Number of decimals in the raw data + 2
Minimum, maximum, range	Number of decimals in the raw data

LL = Lower Limit UL = Upper Limit CI = Confidence Interval
SD = Standard deviation

11.2.7. Other endpoints

Sputum quality criteria

The following criteria and scores will be used:

- >25 squamous epithelial cells/field → sample of bad quality
- 10-25 squamous epithelial cells/field →sample of moderate quality
- < 10 squamous epithelial cells/field → sample of good quality

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

13.1. Lay-out for posting

Template 1A Number of enrolled subjects by country *by using %FREQ_DIS*

		10-10-3-AS N=300	PLACEBO N=300	Total N =600
Characteristics	**Age Categories**	**n**	**n**	**n**
France	40-59 years			
	60-80 years			
	Total			
Germany	40-59 years			
	60-80 years			
	Total			
xxx	40-59 years			
	60-80 years			
	Total			

N = Number of enrolled subjects

n= number of enrolled subjects included in each group or in total for a given age category or for all age categories

Template 2A Number of enrolled subjects by age category *by using %FREQ_DIS*

		10-10-3-AS N=300	PLACEBO N=300	Total N =600
Characteristics	**Categories**	**n**	**n**	**n**
Age category	In utero			
	Preterm newborn infants (gestational age < 37 wks)			
	Newborns (0-27 days)			
	Infants and toddlers (28 days-23 months)			
	Children (2-11 years)			
	Adolescents (12-17 years)			
	Adults (18-64 years)			
	From 65-84 years			
	85 years and over			
	Missing			

N = Number of enrolled subjects

n = number of enrolled subjects included in each group or in total for a given age category or for all age categories

Template 3A Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort) *by using %DROPSUM (OTH=0) Macro:*

	10-10-3-AS	PLACEBO	Total
Number of subjects vaccinated			
Number of subjects completed			
Number of subjects withdrawn			
Reasons for withdrawal :			
Serious Adverse Event			
Non-Serious Adverse Event			
Eligibility criteria not fulfilled (inclusion and exclusion criteria)			
Protocol violation			
Consent withdrawal (not due to an adverse event)			
Migrated/moved from study area			
Lost to follow-up (subjects with incomplete vaccination course)			
Lost to follow-up (subjects with complete vaccination course)			
Sponsor study termination			
Others			

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not complete their last visit

Template 4A Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion *by using %ELIMLIST*

Number of subjects enrolled into the study as well as the number excluded from ATP analyses at Day 21 with reasons for exclusion									
	Total			**10-10-3-AS**		**PLACEBO**		**NOGRP**	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**

Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Template 5A Number (%) of subjects with serious adverse events from the Day 1 till end of the study *by using new CTR_SAE Macro:*

Type of Event	Primary System Organ Class	Preferred Term (CODE)	10-10-3-AS N = 300			PLACEBO N = 300		
			n*	n	%	n*	n	%
SAE	At least one symptom							
	<each SOC>	<each PT>						
Related SAE	At least one symptom							
	<each SOC>	<each PT>						
Fatal SAE	At least one symptom							
	<each SOC>	<each PT>						
Related Fatal SAE	At least one symptom							
	<each SOC>	<each PT>						

N = number of subjects with the administered dose

n* = number of events reported

n/% = number/percentage of subjects reporting the symptom at least once

Template 6A Solicited and unsolicited symptoms experienced by at least 5 % of subjects, classified by MedDRA Primary System Organ Class and Preferred Term including number of events reported - SAE excluded *by using %UNSOL (NIH=5, EVENT=1)*

		10-10-3-AS N = 300			PLACEBO N = 300		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	n*	n	%
At least one symptom							
<each SOC>	<each PT term>						

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of subjects with the administered dose

n* = number of events reported

n/% = number/percentage of subjects reporting the symptom at least once

13.2. Lay-out for CSR

Template 1 Overview of Sets Analyzed

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	n	%	n	%	n	%
All Enrolled set	xxx	100%	xxx	100%	xxx	100%
mTVC	xxx	xx%	xxx	xx%	xxx	xx%
mTVC-PCR	xxx	xx%	xxx	xx%	xxx	xx%
mTVC-Culture	xxx	xx%	xxx	xx%	xxx	xx%
TVC (Exposed Set)						
TVC-Efficacy	xxx	xx%	xxx	xx%	xxx	xx%
TVC-Immunogenicity	xxx	xx%	xxx	xx%	xxx	xx%
TVC-CMI	xxx	xx%	xxx	xx%	xxx	xx%
TVC-Safety	xxx	xx%	xxx	xx%	xxx	xx%
ATP (PPS)						
ATP- Efficacy (clinical)	xxx	xx%	xxx	xx%	Xxx	xx%
ATP- Efficacy (bacteriological)	xxx	xx%	xxx	xx%	xxx	xx%
ATP- Immunogenicity	xxx	xx%	xxx	xx%	xxx	xx%
ATP- CMI	xxx	xx%	xxx	xx%	xxx	xx%

<group description >
n = number of subjects included in each group or in total
% = n/All x 100

Template 2 Study Termination

	10-10-3-AS		PLACEBO		Total	
	n	%	n	%	n	%
Number of subject screened	xxx		xxx		xxx	
Number of subject enrolled	xxx		xxx		xxx	
Number of subject exposed	xxx	xx%	xxx	xx%	xxx	xx%
Number of subject completed	xxx	xx%	xxx	xx%	xxx	xx%
Number of subject withdrawn	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for withdrawn						
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%

<group description >
n = number of subjects included in each group or in total
% = n/All x 100

Template 3 Study Termination, by visit

	10-10-3-AS		PLACEBO		Total	
	n	%	n	%	n	%
Number of subject screened	xxx		xxx		xxx	
Number of subject enrolled	xxx		xxx		xxx	
Number of subject exposed dose 1	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit 1	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation						
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit 2	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation	xxx	xx%	xxx	xx%	xxx	xx%
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
Total number of subject exposed dose 2	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit 3	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation	xxx	xx%	xxx	xx%	xxx	xx%
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
Completed visit x	xxx	xx%	xxx	xx%	xxx	xx%
Primary reason for discontinuation	xxx	xx%	xxx	xx%	xxx	xx%
Exclusion criteria	xxx	xx%	xxx	xx%	xxx	xx%
Protocol violations	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Serious Adverse event Not related to procedure	xxx	xx%	xxx	xx%	xxx	xx%
Consent withdrawal	xxx	xx%	xxx	xx%	xxx	xx%
Moved from study area	xxx	xx%	xxx	xx%	xxx	xx%
Lost to follow up	xxx	xx%	xxx	xx%	xxx	xx%
Other	xxx	xx%	xxx	xx%	xxx	xx%
…..	xxx	xx%	xxx	xx%	xxx	xx%

<group description >
n = number of subjects included in each group or in total
% = n/All x 100

Template 4 Demographic and Baseline Characteristics (and Vital Signs)

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at enrolment (Years)	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-
Age Group	40-59 years	xx	xx.x				
	60-80 years	xx	xx.x				
Gender	Female	xx	xx.x	xx	xx.x	xx	xx.x
	Male	xx	xx.x	xx	xx.x	xx	xx.x
Race	Black or African American	xx	xx.x	xx	xx.x	xx	xx.x
	American Indian or Alaska Native	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - Central / South Asian Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - East Asian Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - Japanese Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Asian - South East Asian Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Native Hawaiian or Other Pacific Islander	xx	xx.x	xx	xx.x	xx	xx.x
	White - Arabic / North African Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	White - Caucasian / European Heritage	xx	xx.x	xx	xx.x	xx	xx.x
	Other	xx	xx.x	xx	xx.x	xx	xx.x
Ethnicity	Hispanic or Latino	xx	xx.x	xx	xx.x	xx	xx.x
	Not Hispanic nor Latino	xx	xx.x	xx	xx.x	xx	xx.x
Exacerbations in previous 12 months	Total AECOPD	xx	xx.x	xx	xx.x	xx	xx.x
	Mild	xx	xx.x	xx	xx.x	xx	xx.x
	Moderate	xx	xx.x	xx	xx.x	xx	xx.x
	Severe	xx	xx.x	xx	xx.x	xx	xx.x
Exacerbations in previous 12 months category	<2	xx	xx.x	xx	xx.x	xx	xx.x
	>=2	xx	xx.x	xx	xx.x	xx	xx.x
Smoking status	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Pack year	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-
GOLD grade	Grade 1	xx	xx.x	xx	xx.x	xx	xx.x
	Grade 2	xx	xx.x	xx	xx.x	xx	xx.x
	Grade 3	xx	xx.x	xx	xx.x	xx	xx.x
	Grade 4	xx	xx.x	xx	xx.x	xx	xx.x
FE1/FVC	>=70	xx	xx.x	xx	xx.x	xx	xx.x
	<70	xx	xx.x	xx	xx.x	xx	xx.x
CMI sub-cohort	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Culture cohort	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation

Note: similar of the above tables is for vital sign but with different parameters (see section 6.1.1)

Template 5 Number of Subject by Country, Center and within CMI and Sputum culture subsets

					Sputum Culture Subset				CMI Subset			
	10-10-3-AS	PLACEBO	Total		10-10-3-AS	PLACEBO	Total		10-10-3-AS	PLACEBO	Total	
Center	**n**	**n**	**n**	**%**	**n**	**n**	**n**	**%**	**n**	**n**	**n**	**%**
France												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Germany												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Belgium												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Italy												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
xxxx												
xxxxxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
……	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx	xx	xx	xx.x
Total												
	xx	xx	xx	100%	xx	xx	xx	100%	xx	xx	xx	100%

<group description >
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100

Template 6 Medical History History

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
System Organ Class Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
SOC 1						
PT 1						
PT 2						
PT 3						
……						
SOC 2						
PT 1						
PT 2						
PT 3						
…..						
SOC 3						
…….						

<group description >
N = number of subjects
n = number of subjects in a given category
SD=Standard Deviation

Template 7 Vaccination History History

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	n	**%**	**n**	**%**	**n**	**%**
Any influenza and/or pneumococcal vaccination						
Influenza vaccination						
pneumococcal vaccination						

<group description >
N = number of subjects
n = number of subjects in a given category
SD=Standard Deviation

Template 8 Vaccine Administration

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Prevaccination temperature (C°)	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-
Temperature location	xxxxx	xx	xx.x				
	xxxxxx	xx	xx.x				
Vaccination Administered	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Vaccination Site	xxxxx	xx	xx.x	xx	xx.x	xx	xx.x
	xxxxxx	xx	xx.x	xx	xx.x	xx	xx.x
	xxxxxx	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation

Template 9 Days on which vaccinations occurred

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Vaccination 1	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Vaccination 2	Yes	xx	xx.x	xx	xx.x	xx	xx.x
	No	xx	xx.x	xx	xx.x	xx	xx.x
Vaccination 2: Days post first vaccination	n	xx		xx		xx	
	Mean	xx.x	-	xx.x	-	xx.x	-
	Median	xx.x	-	xx.x	-	xx.x	-
	SD	x.x	-	x.x	-	x.x	-
	Minimum	xx	-	xx	-	xx	-
	Maximum	xx	-	xx	-	xx	-

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation

Template 10 Days of Blood Samples at Scheduled Visit

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Visit 1 - Day 1						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample Haematology	xx	xx.x	xx	xx.x	xx	xx.x
Visit 2 - Day 31						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	0	0	0	0	0	0
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 31 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 30-45 Days Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 30-45 Days Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Visit 3 - Day 61						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	0	0	0	0	0	0
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 61 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 60-75 Days from Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 60-75 Days from Visit 1	xx	xx.x	xx	xx.x	xx	xx.x
Visit 4 - Day 91						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 91 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 30-45 Days from Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 30-45 Days from Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Visit 6 - Day 271						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	0	0	0	0	0	0
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 271 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 180-210 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 180-210 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 8 - Day 451						
Blood sample for immunogenicity	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for CMI	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample for Biomarker	xx	xx.x	xx	xx.x	xx	xx.x
Blood sample Haematology	0	0	0	0	0	0
Timing of study day 451 blood sample						
No drawn	xx	xx.x	xx	xx.x	xx	xx.x
Drawn within 360-390 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Drawn not within 360-390 Days from Visit 4	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 11 Days of Sputum Samples at Study Visit

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Visit 1 - Day 1						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Visit 4 - Day 91						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 91 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 30-45 Days Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 30-45 Days Visit 3	xx	xx.x	xx	xx.x	xx	xx.x
Visit 5 - Day 181						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 181 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 90-120 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 90-120 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 6 - Day 271						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 271 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 180-210 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 180-210 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 7 - Day 361						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 361 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 270-300 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 270-300 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Visit 8 - Day 451						
Sputum sample for PCR	xx	xx.x	xx	xx.x	xx	xx.x
Sputum sample for Culture	xx	xx.x	xx	xx.x	xx	xx.x
Timing of study day 451 Sputum sample						
No sputum sample	xx	xx.x	xx	xx.x	xx	xx.x
Taken within 360-390 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x
Taken not within 360-390 Days Visit 4	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 12 Duration of Subject participation in the Study

		10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Overall duration of subjects participation (days)	n						
	Mean	xx	xx.x	xx	xx.x	xx	xx.x
	Median	xx	xx.x	xx	xx.x	xx	xx.x
	SD						
	Minimum	xx	xx.x	xx	xx.x	xx	xx.x
	Maximum	xx	xx.x	xx	xx.x	xx	xx.x
Overall duration (days)	<31 days	xx	xx.x	xx	xx.x	xx	xx.x
	31 – <91 days	xx	xx.x	xx	xx.x	xx	xx.x
	91 – <181 days	xx	xx.x	xx	xx.x	xx	xx.x
	181 - <271 days	xx	xx.x	xx	xx.x	xx	xx.x
	361 - <361 days	xx	xx.x	xx	xx.x	xx	xx.x
	361 – <451 days	xx	xx.x	xx	xx.x	xx	xx.x
	>=451 days	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 13 Protocol deviation summary /exclusion summary

	10-10-3-AS N=300		PLACEBO N=300		Total N=600	
	Value or n	%	Value or n	%	Value or n	%
Any protocol deviation	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 1	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 2	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 3	xx	xx.x	xx	xx.x	xx	xx.x
Deviation 4	xx	xx.x	xx	xx.x	xx	xx.x
……	xx	xx.x	xx	xx.x	xx	xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Note: similar of the above tables is for Exclusion with each population in raw before the list of exclusions

Template 14 Percentage of subjects with antibody concentration above assay cut-off and vaccine group differences

		10-10-3-AS N=300				PLACEBO N=300				Difference N=600	
Strain	**Time**	N	n	%	95% CI	N	n	%	95% CI	%	95% CI
Anti – PD Antibody > 153	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
Anti – PE Antibody > 8	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
Anti – PilA Antibody > 7	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
Anti – USPA 2 igG Antibody > 18	Day 1 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 31	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 61 (Pre dose)	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 91	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 271	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x
	Day 451	xxx	xxx	xx.x	xx.x - xx.x	xxx	xxx	xx.x	xx.x - xx.x	xx.x	xx.x - xx.x

<group description >
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100

Template 15 Geometric mean Antibody concentration and Vaccine Ratios

		10-10-3-AS N=300		PLACEBO N=300		GMTs Ratio N=600	
Time	**Parameters**	**Value or n**	**95% CI**	**Value or n**	**95% CI**	**Value or n**	**95% CI**
Day 1 (Pre dose)	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 31	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 61 (Pre dose)	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 91	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 271	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 451	GMT	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-

<&footnote1.>
<group description >
GMC = geometric mean antibody concentration
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
CI=Confidence interval

Template 16 Geometric mean Ratio and Vaccine Ratios

		10-10-3-AS N=300		PLACEBO N=300		GMRs Ratio N=600	
Time	**Parameters**	**Value or n**	**95% CI**	**Value or n**	**95% CI**	**Value or n**	**95% CI**
Day 31 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 61 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 91 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 271 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-
Day 451 / Day 1	GMR	xx.xx	xx.x – xx.x	xx.xx	xx.x – xx.x	x.x	x.x – x.x
	SD	xx.x	-	xx.x	-	-	-
	Median	xx.x	-	xx.x	-	-	-
	Minimum	Xx	-	Xx	-	-	-
	Maximum	Xx	-	Xx	-	-	-
	n	xxx	-	xxx	-	-	-

<&footnote1.>
<group description >
GMR = geometric mean antibody concentration ratio
N = number of patients. n = number of patients in a given category
Value = value of the considered parameter
CI=Confidence interval

Template 17 Descriptive statistics of PD, PE, PilA, UspA2 specific CD4+ T cells expressing at least <two markers> per million cells, using background reduced frequency data

			10-10-3-AS N=	PLACEBO N=
Simulation	**TIMING**	**Parameters**	**Value**	**Value**
Hi NTHi PD	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
Hi NTHi PE	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx

			10-10-3-AS N=	PLACEBO N=
Simulation	**TIMING**	**Parameters**	**Value**	**Value**
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
Hi NTHi PilA	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		n	xx	xx

			10-10-3-AS N=	**PLACEBO N=**
Simulation	**TIMING**	**Parameters**	**Value**	**Value**
M catarrhalis UspA2	Day 1 (pre-dose)	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 91	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 271	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		Maximum	xxx	xxx
	Day 451	n	xx	xx
		Mean	xx.x	xx.x
		SD	xx.xx	xx.xx
		Minimum	x	x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xxx.x	xxx.x
		n	xx	xx

<&footnote1.>
<group description >
N = number of subjects
Value = value of the considered parameter
SD = Standard deviation
Q1,Q3 = First and third quartiles

Template 18 Summary of the number of < type>AECOPD

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		xxx				
Exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		xxxx				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 19 Summary of the number of AECOPDs by severity

				10-10-3-AS N=		PLACEBO N=	
Severity	**Timings**			**Value or n**	**%**	**Value or n**	**%**
Mild	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
Moderate	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				

				10-10-3-AS N=		PLACEBO N=	
Severity	**Timings**			**Value or n**	**%**	**Value or n**	**%**
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
Severe	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				

				10-10-3-AS N=		PLACEBO N=	
Severity	**Timings**			**Value or n**	**%**	**Value or n**	**%**
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
Overall total	Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				
		Exacerbation rate	Mean				
			SD				
			Q1				
			Median				
			Q3				
			Minimum				
			Maximum				
		Number of exacerbations	00				
			01				
			02				
			03				
			04				
			05				
	Any exacerbation after 1 month post Dose 2	Total number of subjects	Sum				
		Total number of exacerbations	Sum				
		Total exposure time in days	Sum				
		Overall exacerbation rate	Mean				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 20 Vaccine Efficacy for <type> AECOPDs

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**Time (year)**	**n/T**	**87% CI**	**95% CI**	**%**	**87% CI**	**95% CI**	**P-Value**
<Moderate and severe> AECOPDs	10-10-3-AS01E										
	PLACEBO										

<&footnote1.>
<group description >
n = number of subjects in a given category
Time (year) = sum of follow-up period expressed in year
n/T = person-year rate in each group

Template 21 Parameter estimation following Vaccine Efficacy of <type> AECOPDs

Covariate	Estimate	87% CI	95% CI	P-Value
Country				
Age				
GOLD				
Exacerbation History				

<&footnote1.>

Template 22 Summary of the number of < type>AECOPD, by sub-period

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Any exacerbation before 1 month post Dose 2	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
Any exacerbation after 1 month post Dose 2 until month 4	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
Any exacerbation before 1 month post Dose 2 until month 7	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Any severity exacerbation after 1 month post Dose 2 until month 10	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 23 Average length of <type> AECOPD

		10-10-3-AS N=	PLACEBO N=
Timings	**Statistics**	**Value**	**Value**
Any exacerbation before 1 month post Dose 2	N		
	Mean		
	SD		
	Median		
	Q1		
	Q3		
	Minimum		
	Maximum		
Any exacerbation after 1 month post Dose 2	N		
	Mean		
	SD		
	Median		
	Q1		
	Q3		
	Minimum		
	Maximum		

<group description >
N = number of exacerbations with calculated duration in a given category
Value = value of the considered parameter, SD = Standard deviation

Template 24 Average length of <type> AECOPD, by Severity

			10-10-3-AS N=	PLACEBO N=
Exacerbation severity	**Timings**	**Statistics**	**Value**	**Value**
Mild	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
Moderate	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
Severe	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		

			10-10-3-AS N=	PLACEBO N=
Exacerbation severity	**Timings**	**Statistics**	**Value**	**Value**
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
Any severity exacerbations	Any exacerbation before 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		
	Any exacerbation after 1 month post Dose 2	N		
		Mean		
		SD		
		Median		
		Q1		
		Q3		
		Minimum		
		Maximum		

<group description >
N = number of exacerbations with calculated duration in a given category
Value = value of the considered parameter
SD = Standard deviation

Template 25 Hazard Rate for <type> AECOPD

Parameter	DF	Parameter Estimate	SE	P-value	Hazard Ratio
Vaccine group					
Age					
GOLD					
History of AECOPD					

<Parameters description >
DF = degree of freedom
SE = standard error

Template 26 Proportion of Patients with Sputum Samples Positive for Bacterial Pathogens at any stable or exacerbation visit

		10-10-3-AS N=						PLACEBO N=					
		Patients			Sputum positive			Patients			Sputum positive		
Bacteria	Visit	N	n	%	ns	%	95% CI	N	n	%	ns	%	95% CI
Any	Enrolment												
	Any stable visit												
	Any AECOPD visit												
H. influenzae	Enrolment												
	Any stable visit												
	Any AECOPD visit												
M. catarrhalis	Enrolment												
	Any stable visit												
	Any AECOPD visit												
S. pneumoniae	Enrolment												
	Any stable visit												
	Any AECOPD visit												
S. aureus	Enrolment												
	Any stable visit												
	Any AECOPD visit												
P. aeruginosa	Enrolment												
	Any stable visit												
	Any AECOPD visit												
K. pneumoniae	Enrolment												
	Any stable visit												
	Any AECOPD visit												
A. baumannii	Enrolment												
	Any stable visit												
	Any AECOPD visit												

N = number of patients in each visit
n= number of patients positive to bacteria
% = percentage of patients with sputum samples positive for bacterial pathogens
ns = number of sputum samples positive to bacteria

Template 27 Subjects with at least one Solicited Adverse Events

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
Dose 2	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
Overall/dose	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
Overall/subject	10-10-3-AS	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	PLACEBO	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

<group description >
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 28 Subjects with Solicited Local Adverse Events, Maximum Event Severity and Grade 3 Events

		10-10-3-AS					PLACEBO				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										
Dose 2											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										
Overall/dose											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										
Overall/subject											
Pain	All										
	Grade 3										
Redness (mm)	All										
	> 100										
Swelling (mm)	All										
	> 100										

<group description >
For each dose and overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Same lay-out for General symptoms (see section 6.5.1.1for list for local or general solicited adverse events)

Template 29 Body Temperature Measurements - Maximum Event Severity From Day 1 Through Day 7 Following each Vaccination

		10-10-3-AS					PLACEBO				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Temperature/(Oral) (°C)	<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										
Dose 2											
Temperature/(Oral) (°C)	<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										
Overall/dose											
Temperature/(Oral) (°C)	<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										
Overall/subject											
Temperature/(Oral) (°C)	<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										

<group description >

For each dose and overall/subject:

N = number of subjects with at least one documented dose

n/% = number/percentage of subjects reporting the symptom at least once

For Overall/dose:

N = number of documented doses

n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 30 Concomitant Medication and Vaccination

	10-10-3-AS N=		PLACEBO N=	
Generic Drug Name	**n**	**%**	**n**	**%**
Term 1				
Term 2				
Term 3				
Term 4				
xxxx				

<group description >
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

Template 31 Subjects With Unsolicited Adverse Events After Any Vaccination sorted by SOC

		10-10-3-AS N=		PLACEBO N=	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**n**	**%**
At least one Adverse Event					
SOC 1	PT 1				
	PT 2				
	PT 3				
SOC 2	PT 1				
	PT 2				
	PT 3				
SOC 3	PT 1				
	PT 2				
	PT 3				

<group description >
At least one symptom = at least one Adverse Event experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

Template 32 Number and Percentage of sputum samples per quality score, collected at each Stable and Exacerbation visit

		10-10-3-AS N=		PLACEBO N=	
Visit	Quality	n	%	n	%
Visit 1 (Day 1)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
Visit 4 (Day 91)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
Visit 5 (Day 181)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
Visit x (Day xx)	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
AECOPD Visit 1	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				
AECOPD Visit x	Bad quality				
	Moderate quality				
	Good quality				
	Total sputum collected				

<group description >
N= Number of subjects
n = number of sputum
%= percentage of sputum in each category (n/total n)

Template 33 Proportion of Patients with Sputum Samples Positive for Bacterial Pathogens at any stable or exacerbation visit, by Country

		Any stable visit												Any AECOPD visit					
		10-10-3-AS N=						PLACEBO N=						10-10-3-AS N=			PLACEBO N=		
		Patients			Sputum			Patients			Sputum			Patients			Sputum		
Bacteria	Country	N	n	%	ns	sp	%	N	n	%	ns	sp	%	N	n	%	ns	sp	%
Any	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
H. Influenzae	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
M. catarrhalis	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
S. pneumoniae	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		
xxx	France																		
	Germany																		
	Belgium																		
	Italy																		
	Spain																		
	UK																		
	USA																		
	Canada																		

<group description >
N = number of patients in each visit
n= number of patients positive to bacteria
% = percentage of patients with sputum samples positive for bacterial pathogens
ns = number of sputum samples
np= number of sputum samples positive to bacteria

Template 34 Proportion of patients with sputum samples positive for bacterial pathogens by visit.

		10-10-3-AS N=				PLACEBO N=			
Bacteria	Visit / Day	N	n	%	95% CI	N	n	%	95% CI
Any	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD Visit 3								
	AECOPD >3								
. H. Influenzae	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD 3								
	AECOPD >3								
M. catarrhalis	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD Visit 3								
	AECOPD >3								
S. pneumoniae	Visit 1/ Day 1								
	Visit 4/ Day 91								
	Visit 5/Day 181								
	Visit 6/Day 271								
	Visit x / Day xxx								
	AECOPD Visit 1								
	AECOPD Visit 2								
	AECOPD Visit 3								
	AECOPD >3								
xxx	…..								

<group description >
N = number of patients providing a sputum sample
n = number of sputum samples positive for bacterial pathogen
% = percentage of patients with sputum samples positive for bacterial pathogens

Template 35 Sputum sample collection, by method

		Day 1				Day 91				Day x			
		10-10-3-AS N=		**PLACE N=**		**10-10-3-AS N=**		**PLACE N=**		**10-10-3-AS N=**		**PLACE N=**	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Has a sputum sample collected?	NO												
	YES												
How was the sputum collected?	Spontaneous												
	Induced 0.9%												
	Induced 3%												
Was an antibiotic administered before sputum sample collection?	NO												
	YES												
Number of hours since start of antibiotic administration	Mean												
	SD												
	Median												
	Q1												
	Q3												
	Minimum												
	Maximum												

<group description >
N = number of patients
n = number of patients in a given category
Value = value of the considered parameter
% = n / number of patients with available results x 100
SD = Standard deviation Q1, Q3 = first and third quartiles

Template 36 Proportion of sputum samples at pre-vaccination, after 2 doses and at any exacerbation visit that are positive for specific pathogens overall and by bacterial species

		10-10-3-AS N=					PLACEBO N=				
					95% CI					95% CI	
Bacteria	**Timings**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Any	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
H. Influenzae	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
M. catarrhalis	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
S. pneumoniae	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										
xxx	At pre-vaccination visit (Day 1)										
	1 month after 2nd dose (Day 91)										
	At Any exacerbation visit before Dose 2										
	At Any exacerbation visit after Dose 2										
	At Any exacerbation visit at Day 181										
	At Any exacerbation visit at Day 271										
	At Any exacerbation visit at Day 361										
	At Any exacerbation visit at Day 451										

<group description >
N = number of sputum samples
n = number of sputum samples in a given category
% = n/Number of sputum samples x 100
Hi = Haemophilus influenza

Template 37 Simultaneous bacterial presence in sputum at pre-vaccination, after 2 doses and at any exacerbation visit

	10-10-3-AS																	
	At pre-vaccination visit			After 2 doses (Day 91)			At Any exacerbation visit before Dose 2			At Any exacerbation visit after Dose 2			At Any exacerbation visit at Day 181			At Any exacerbation visit at Day 271		
Bacterial combination	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Hi																		
Hi+Mcat																		
Hi+Mcat+Sp																		
Hi+Oth																		
Hi+Psa																		
Hi+Sp																		
Hi+Sta																		
Hi+Sta+Oth																		
Mcat																		
Mcat+Oth																		
Mcat+Psa																		
Mcat+Sp																		
Mcat+Sta																		
Oth																		
Psa																		
Psa+Oth																		
Sp																		
Sp+Oth																		
Sta																		
None																		

<group description >
N = number of sputum samples
n = number of sputum samples in a given category
% = n/Number of sputum samples x 100

All visits and same table for control

Template 38 Simultaneous selected bacterial presence in sputum pre-vaccination, after 2 doses and at any exacerbation visit for Hi and Mcat

	10-10-3-AS																	
	At pre-vaccination visit			After 2 doses (Day 91)			At Any exacerbation visit before Dose 2			At Any exacerbation visit after Dose 2			At Any exacerbation visit at Day 181			At Any exacerbation visit at Day 271		
Bacterial combination	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Hi alone																		
Mcat alone																		
Hi or Mcat mixed																		
Other																		
None																		

<group description >
N = number of sputum samples
n = number of sputum samples in a given category
% = n/Number of sputum samples x 100

All visits and same table for control

Template 39 Summary of the number of exacerbations having sputum containing any bacterial pathogens

			10-10-3-AS													
			Any		Hi		Mcat		Sp		Sta		Psa		Other	
Timings			**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Any exacerbation before 1 month post Dose 2	N	Sum														
	Number of AECOPD	Sum														
	Total exposure (days)	Sum														
	Overall AECOPD rate	Mean														
	Exacerbation rate	Mean														
		SD														
		Median														
		Q1														
		Q3														
		Minimum														
		Maximum														
	Number of exacerbations	00														
		01														
		02														
		03														
Any exacerbation after 1 month post Dose 2	N	Sum														
	Number of AECOPD	Sum														
	Total exposure (days)	Sum														
	Overall AECOPD rate	Mean														
	Exacerbation rate	Mean														
		SD														
		Median														
		Q1														
		Q3														
		Minimum														
		Maximum														
	Number of exacerbations	00														
		01														
		02														
		03														
		x														

<group description >
N = Total number of subjects

Same lay-out for the 'by Country' table

Template 40 Frequencies of semi-quantitative bacteriological load

			10-10-3-AS										PLACEBO									
			Any		Hi		Mcat		Sp		xxx		Any		Hi		Mcat		Sp		xxx	
Timings			**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Day 1	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
Day 91	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
Day 181	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
xxxx	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
Exacerbation visit 1	Negative Load																					
	Positive Load	Few scattered																				
		+																				
		++																				
		+++																				
	Not assessable																					
xxxxx																						

<group description >

Note: if not enough space the two groups can be split (as lay-out 37, 38 and 39)

Template 41 Use of medication to treat AECOPD

		10-10-3-AS N=		PLACEBO N=	
Type		n	%	n	%
Number of medication	0				
	1				
	2				
	3				
	4				
	>4				
Indication	Chronic use COPD				
	Chronic use Other disorders				
	Exacerbation				
	Rescue medication				
Type of treatment	Concomitant medication				
	Treatment given for COPD (standard of care)				
	Additional treatment for COPD (not standard of care).				

<group description >

Template 42 Percentage of Subjects With Healthcare Utilization

		10-10-3-AS N=		PLACEBO N=	
Characteristics		**Value**	**%**	**value**	**%**
Healthcare Use					
Healthcare Use Frequency	0				
	1				
	2				
	3				
Specific Healthcare Use	General practitioner (not the study doctor)	**			
	Respiratory consultant				
	Other specialist				
	Emergency				
	Pulmonary rehabilitation program				
	Nutrition advice				
Hospitalization		***			
	Intensive Care	****			
	General Ward				

<group description >
n = number of subjects in a given category
Value = value of the considered parameter
*number of subjects who used health care consequently to an exacerbation
** number of subjects who went to the GP consequently to an exacerbation
*** number of subjects who have been hospitalized consequently to an exacerbation
**** number of subjects who have been admitted to intensive care consequently to an exacerbation
%=based on total number of subjects and not subjects in each category

Template 43 Pulmonary function test by Visit

Visit		Screening		Day 271		Day 451	
Spirometer Parameter		**10-10-3-AS N=**	**PLACEBO N=**	**10-10-3-AS N=**	**PLACEBO N=**	**10-10-3-AS N=**	**PLACEBO N=**
FEV1 (L)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEV1 (% of predicted)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FVC (L)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FVC (% of predicted)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEV1/FVC	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
PEF(L/sec)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEF25-75%	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
FEF25-75% (% of predicted)	n						
	Mean						
	SD						
	Median						
	Minimum						
	Maximum						

<group description >

n = number of subjects in a given category; SD = Standard deviation,

FEV1 = Forced Expiratory Volume of air in 1 second (L), FVC = Forced Expiratory Vital Capacity (L), PEF= Peak Expiratory Flow (L/sec), FEF25-75%= Forced expiratory flow between 25% and 75% of FVC (L/sec)

Template 44 Descriptive statistics of biomarker

		10-10-3-AS N=	PLACEBO N=
Fibrinogen			
Day 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
Day 451	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 2	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit x	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
hsCRP			
Day 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
Day 451	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		

		10-10-3-AS N=	PLACEBO N=
AECOPD Visit 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 2	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit x	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
IP-10.			
Day 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
Day 451	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 1	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		
AECOPD Visit 2	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		

		10-10-3-AS N=	**PLACEBO N=**
AECOPD Visit x	Mean		
	SD		
	Minimum		
	Q1		
	Median		
	Q3		
	Maximum		

<group description >
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

Template 45 Daily Report for Solicited Adverse Events

10-10-3-AS							
Vaccination Number	**Category**	**Within 60 Min**	**Day 1**	**Day 2**	**Day …**		**Day 7**
Solicited Local Adverse Event: Pain at injection site							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
2	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Any	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Solicited Local Adverse Event: Redness at injection site							
1	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
2	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
Any	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
Solicited Local Adverse Event: xxx							
1	n						
	Any						
	<20 mm						
	20 - ≤ 50						
	51 - ≤ 100						
	>100						
xxxx							

Solicited General Adverse Event: Headache							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
2	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Any	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Solicited General Adverse Event: xxxx							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
xxxx							
PLACEBO							
Solicited Local Adverse Event: Pain at injection site							
1	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
2	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
Any	n						
	Any						
	None						
	Mild						
	Moderate						
	Severe						
xxxx							

<group description >

Template 46 Solicited and Unsolicited Adverse Events

		10-10-3-AS N=				PLACEBO N=			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom									
xxxx									

<group description >
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 47 Solicited and Unsolicited Adverse Events, by Vaccination

		10-10-3-AS N=				PLACEBO N=			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Vaccination 1									
At least one symptom									
xxxx									
Vaccination 2									
xxxxx									

<group description >
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Note: Similar lay-out for the 'by Severity' table

Template 48 Summary of EXACT-pro Average Scores

		10-10-3-AS N=300	PLACEBO N=300	Difference N=600
Timing	**Parameters**	**Average Score**	**Average Score**	**Average Score**
Screening	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*			
Treatment	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*	-	-	
Exacerbation	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*	-	-	
Follow –up:	N			
	Mean			
	SD			
	Median			
	Minimum			
	Maximum			
	95% CI			
	p-value*			

<group description >
<&footnote >

Template 49 Summary of <questionnaire> scores

		10-10-3-AS N=300	PLACEBO N=300	Difference N=600
Timing	**Parameters**	**Score**	**Score**	**Score**
Screening	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*	-	-	
Day 271	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*	-	-	
Day 451	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*	-	-	
Any Stable Visit	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*			
Any AECOPD Visit	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	p-value*			

		10-10-3-AS N=300	PLACEBO N=300	Difference N=600
Timing	**Parameters**	**Score**	**Score**	**Score**
Difference between Day 271 – screening	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	Maximum			
	p-value**			
Difference between Day 451 – screening	N			
	Mean			
	SD			
	Minimum			
	Q1			
	Median			
	Q3			
	Maximum			
	Maximum			
	p-value**			

<group description >
<&footnote >

Note 1: For the by Severity and by number table lay-out will include an additional raw for severity or number of AECOPD

Note 2: For the SGRQ-C lay-out will include an additional raw for the component scores

Template 50 Number and Percentage of sputum samples by Neutrophils Cells count, collected at each Stable and Exacerbation visit

		10-10-3-AS N=		PLACEBO N=	
Visit	Quality	n	%	n	%
Visit 1 (Day 1)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
Visit 4 (Day 91)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
Visit 5 (Day 181)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
Visit x (Day xx)	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
AECOPD Visit 1	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				
AECOPD Visit x	<10				
	10 - 25				
	>25				
	Unknown				
	Not Done				

<group description >
N= Number of subjects
n = number of sputum
%= percentage of sputum in each category (n/total n)

Template 51 Bacteria direct smear collected at each Stable and Exacerbation visit

		10-10-3-AS N=		PLACEBO N=	
Visit	Quality	n	%	n	%
Visit 1 (Day 1)	Gram-positive Diplococci				
	Gram-positive Cocci				
	Gram-positive rods Bacilli				
	Gram-negative Cocci				
	Gram-negative Bacilli				
	Yeasts				
	Mycelium				
	Yeasts with Pseudomycelium				
	Mixed flora				
	No bacteria				
	Other				
	Not done				
Visit x (Day xx)	Gram-positive Diplococci				
	Gram-positive Cocci				
	Gram-positive rods Bacilli				
	Gram-negative Cocci				
	Gram-negative Bacilli				
	Yeasts				
	Mycelium				
	Yeasts with Pseudomycelium				
	Mixed flora				
	No bacteria				
	Other				
	Not done				
AECOPD Visit x	Gram-positive Diplococci				
	Gram-positive Cocci				
	Gram-positive rods Bacilli				
	Gram-negative Cocci				
	Gram-negative Bacilli				
	Yeasts				
	Mycelium				
	Yeasts with Pseudomycelium				
	xxxx				
	xxxx				

<group description >
N= Number of subjects
n = number of sputum
%= percentage of sputum in each category (n/total n)

Template 52 Summary of the Number of Moderate and Severe AECOPD During Entire Study Period

			10-10-3-AS N=		PLACEBO N=	
Timings			**Value or n**	**%**	**Value or n**	**%**
Any exacerbation during entire study period	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Minimum				
		Q1				
		Median				
		Q3				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 53 Summary of the Number of any AECOPD During Entire Study Period, by severity

			10-10-3-AS N=		PLACEBO N=	
Severity			**Value or n**	**%**	**Value or n**	**%**
Mild	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		…				
Moderate	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		…				
Severe	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		02				
		03				
		…				

			10-10-3-AS N=		PLACEBO N=	
Severity			**Value or n**	**%**	**Value or n**	**%**
Any Severity	Total number of subjects	Sum				
	Total number of exacerbations	Sum				
	Total exposure time in days	Sum				
	Overall exacerbation rate	Mean				
	Exacerbation rate	Mean				
		SD				
		Q1				
		Median				
		Q3				
		Minimum				
		Maximum				
	Number of exacerbations	00				
		01				
		….				

<&footnote1.>
<group description >
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = Standard deviation

Template 54 Average length of <type> AECOPD During Entire Study Period

		10-10-3-AS N=	PLACEBO N=
Timings	**Statistics**	**Value**	**Value**
Any exacerbation During entire study period	N		
	Mean		
	SD		
	Median		
	Q1		
	Q3		
	Minimum		
	Maximum		

<group description >
N = number of exacerbations with calculated duration in a given category
Value = value of the considered parameter, SD = Standard deviation

Note: similar lay-out for the by severity table, adding column with severity

Template 55 Summary of Baseline Haematology profile

		10-10-3-AS N=	PLACEBO N=
White Blood Cells			
Leukocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Neutrophils	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Lymphocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Eosinophils	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Basophils	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Monocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Red Blood Cells			
Erythrocytes	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		
Hemoglobin	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		

		10-10-3-AS N=	PLACEBO N=
Platelets	N		
	Mean		
	Median		
	SD		
	Minimum		
	Maximum		

Template 56 Percentage of subjects having Hematology parameter below or above normal ranges

		10-10-3-AS N=	PLACEBO N=
White Blood Cells			
Leukocytes	Below		
	Within		
	Above		
	Total		
Neutrophils	Below		
	Within		
	Above		
	Total		
Lymphocytes	Below		
	Within		
	Above		
	Total		
Eosinophils	Below		
	Within		
	Above		
	Total		
Basophils	Below		
	Within		
	Above		
	Total		
Monocytes	Below		
	Within		
	Above		
	Total		
Red Blood Cells			
Erythrocytes	Below		
	Within		
	Above		
	Total		
Haemoglobin	Below		
	Within		
	Above		
	Total		
Platelets	Below		
	Within		
	Above		
	Total		

<group description >
See Listing 16.2.8.1 for Normal Ranges Definitions

Figure 3 Survival curve, Time to First AECOPD

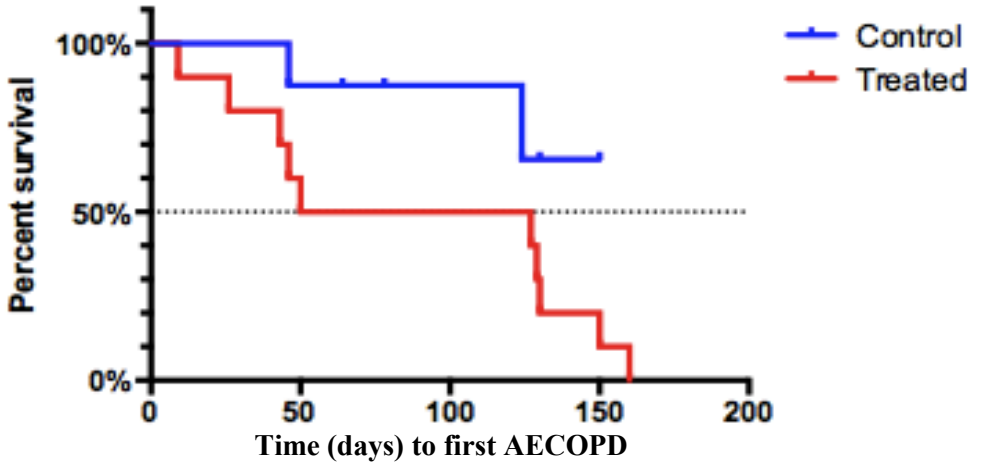


Figure 4 Reverse cumulative distribution curve for <each antigen> antibody concentration before vaccination and one month after the second dose

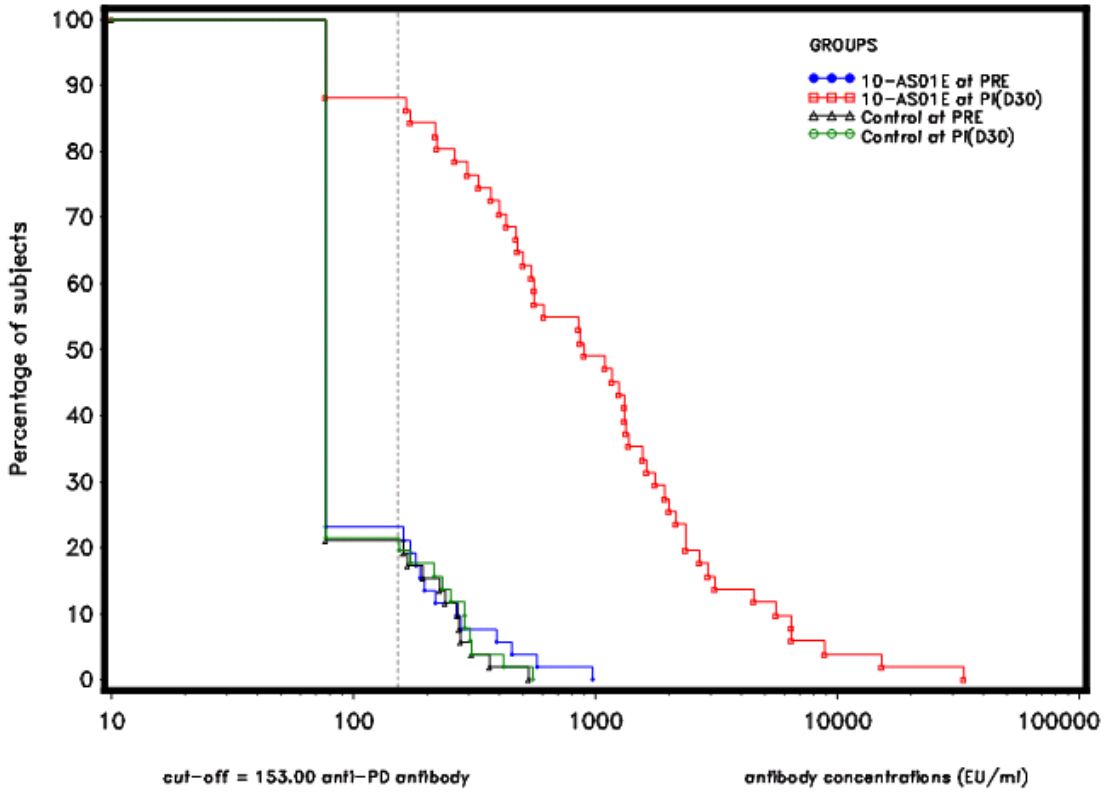


Figure 5 **Box-plots of < each antigen > specific CD4+ T(CD8+T) cells expressing at <specific marker >**

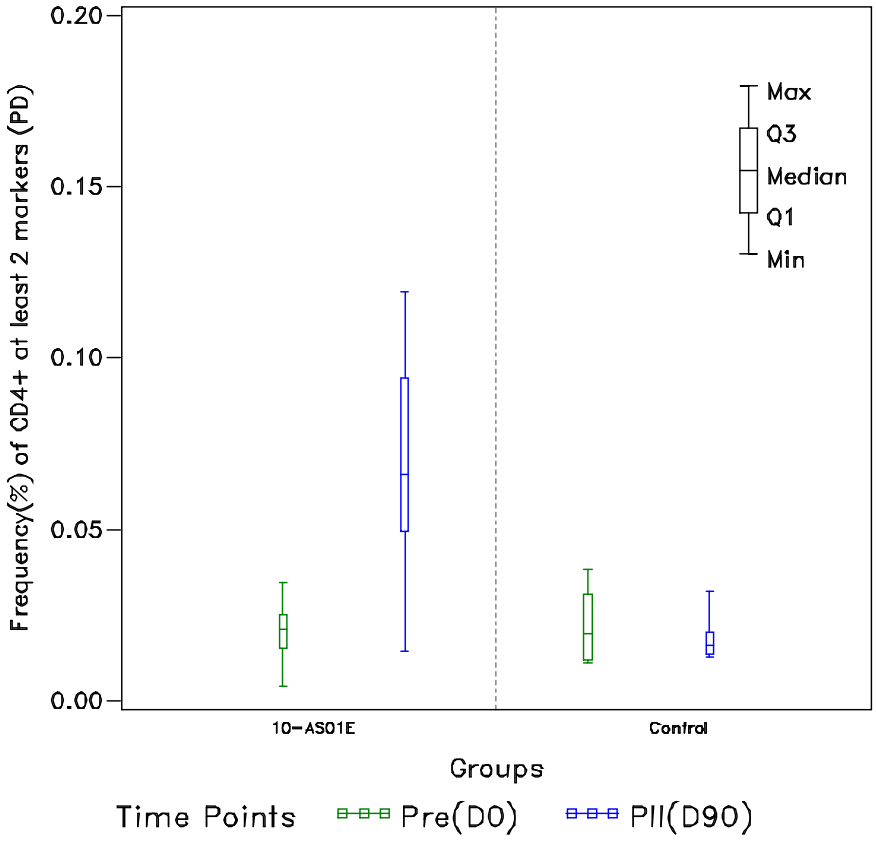


Figure 6 **Pie chart of simultaneous bacterial presence in sputum**

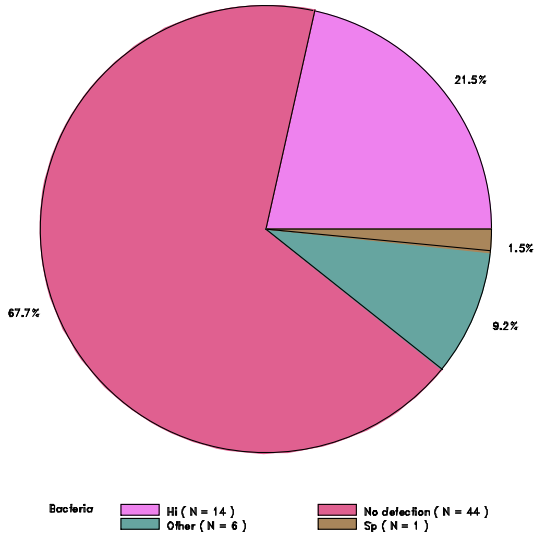


Figure 7 Average Score for EXACT-PRO per each visit period

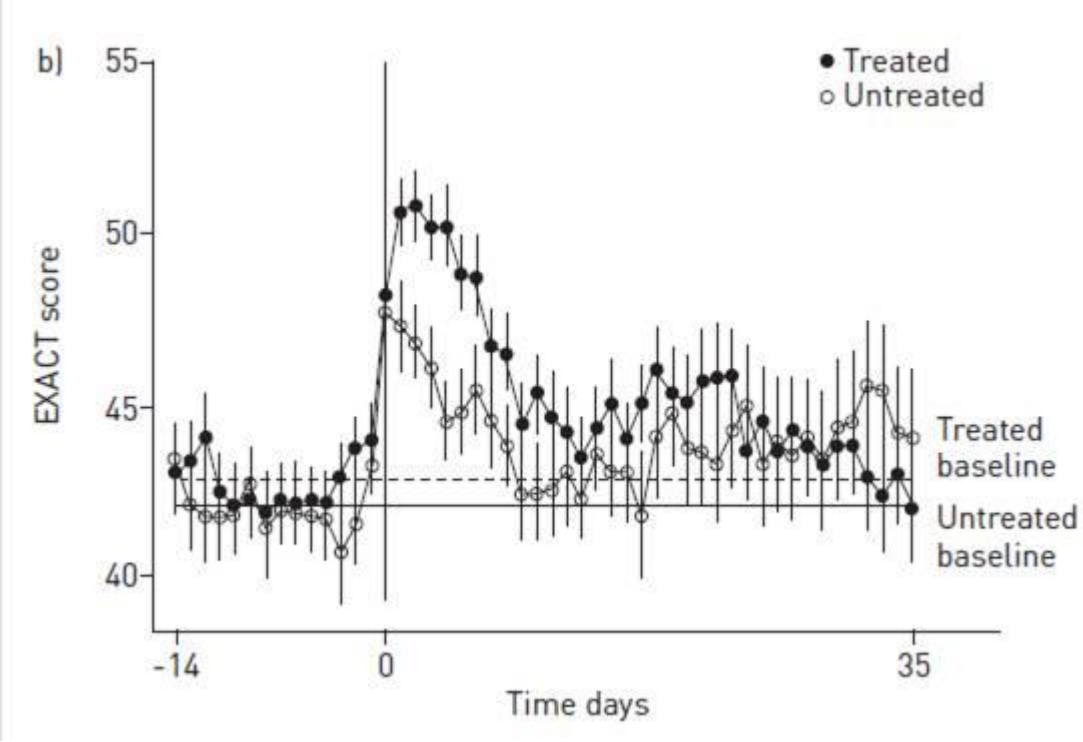


Figure 8 Daily report for Solicited Adverse Events