Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'institut 89,
1330 Rixensart

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) multi-antigen vaccine consisting of three conserved surface proteins (PD, PE and PilA) from *Haemophilus influenzae* and one conserved surface protein (UspA2) from Mcat (GSK3277511A)
Other Study vaccine	• Control: Placebo
eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
Investigational New Drug (IND) number	16531
EudraCT number	2017-000880-34
Date of protocol	Final Version 2: 07 June 2017
Date of protocol amendment/administrative change	Amendment 1 Final: 30 November 2017 Administrative Change 1 Final: 15 December 2017 Amendment 2 Final: 27 March 2019
Title	An observer-blind study to evaluate the efficacy, safety, reactogenicity and immunogenicity of the GSK Biologicals' investigational vaccine GSK3277511A when administered to COPD patients.
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 month schedule in COPD patients aged 40 to 80 years with a previous history of acute exacerbation (AECOPD).
Co-ordinating author (Amended 27 March 2019)	PPD ***(Amendment 2 onward)*** (XPE Pharma & Science for GSK Biologicals)
Contributing authors	• PPD (Clinical & Epidemiology Project Lead)

eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
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Contributing authors (continued) (Amended 27 March 2019)	• PPD ***(Senior Clinical Research & Development Lead)*** PPD ***(Amendment 2 onward) (Clinical Research & Development Lead)*** • PPD (Lead Statistician) • PPD (Director Clinical Statistics) • PPD ***(Amendment 2 onward) (Study Statistician)*** • PPD ***(Amendment 2 onward)*** (Study Delivery Leads) • PPD (CLS Clinical Read-out Team Leader) • PPD (CLS Study manager) • PPD ***(Amendment 2 onward)*** (Clinical Trials Supply Manager) • PPD (Clinical Safety Representative) • PPD (Oversight Data Manager) • PPD (Study Data Manager) • PPD ***(Amendment 2 onward)*** (Regulatory Affairs Representatives) • PPD (Global Patents Representative) • PPD (Vaccine Development Lead)

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
IND number	16531
EudraCT number	2017-000880-34
Date of protocol amendment	Amendment 2 Final: 27 March 2019
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 month schedule in COPD patients aged 40 to 80 years with a previous history of acute exacerbation (AECOPD).
Sponsor signatory	Ashwani Kumar Arora Clinical & Epidemiology Project Lead
Signature	
Date	

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Protocol Amendment 2 Rationale

Amendment number: Amendment 2

Rationale/background for changes:

- The coordinating and contributing authors on (pages 1& 2) were updated to reflect the current team in this Amendment.
- Copyright statement (page 2), date updated in this Amendment.
- Glossary (pages 32 and 33), definitions were added for acquisition and apparition in this Amendment.
- The text in Section 1.4.1 (page 42) related to spirometry was aligned with the wording used in the informed consent form (ICF) in this Amendment.
- The text in Section 4.1.1 (page 50) was aligned with the wording used in the inclusion criteria in this Amendment.
- The text in footnote c of Table 6 (page 61) was amended to clarify that pregnancy tests will be performed in on all females of childbearing potential in this Amendment.
- The text in Section 6.9.14 (page 67) was aligned with the changes made to Footnote c for Table 6 in this Amendment.
- Clarification was provided in Section 6.9.21, Recording of AEs, SAEs, pregnancies and pIMDs (page 70) in this amendment (minor change to wording)
- Table 10 (page 75) the new ELISA cut-offs were added in this Amendment as there are now qualified assays.
- In Section 9.4.1 (page 100) text was added to clarify that AECOPD classified as SAE occurring within a defined time period should also be recorded in the eCRF as “AECOPD visit” or as “Missed AECOPD visit”
- Synopsis (page 11) referring to Section 2.3 Tertiary objectives (page 44), and Synopsis (page 17) referring to Section 11.3 Tertiary endpoints (page 110) has been updated to include the analyses of acquisition and apparition of bacteria in culture and PCR.
- Clarification of the correct process to report pIMDs during the study was included in Section 9.4.5 Reporting of pIMDs to GSK Biologicals (page 102) in this Amendment.
- Clarification was provided in Section 10.2.2 Subject (page 108) regarding the withdrawal procedure in this Amendment.
- In Section 11.3 (Tertiary Endpoints, page 110), “acquisition and apparition” was added to the endpoints.
- In Section 11.8, Analysis of Efficacy, Efficacy – Clinical (page 118) the text was modified to correct an inconsistency within the section, clarifying that all efficacy clinical endpoints will be computed with 95% confidence intervals with the

exception of the primary clinical efficacy endpoint that will also be computed with 87% confidence interval. There will be no change in the interpretation of the analysis compared to the previous version of the Protocol.

- In Section 11.8, Analysis of Efficacy, Efficacy – Bacteriological Endpoint (PCR), (pages 119-120) text was added to clarify the timepoints for the analysis.
- In Section 11.8, Analysis of Efficacy, Efficacy – Bacteriological Endpoint (culture), (page 120) text was added to clarify the timepoints for the analysis.
- In Section 11.8 Analysis of Efficacy (page 120) a section was added regarding the definitions of acquisition and apparition and information regarding the analysis was added in this Amendment
- Appendix A Laboratory Assays (page 136), the new ELISA cut-offs were added in this Amendment as there are now qualified assays.
- Appendix B Clinical Laboratories, Table 26 (page 137) CEVAC and DDL added to the table of outsourced laboratories in this Amendment.
- Minor corrections; e.g. correction of minor typographical and formatting errors were made for clarity in Section 4.1.1 (from eDiaries to eDiary), Section 6.7 (from SP to SPM), Section 9.1.3 (from eDiaries to eDiary), Section 11.4 (Table 23 and Table 24 [*et al* removed from footnote Keen *et al.* (2007) to Keen, 2007]), Sections 11.5.4 (Per protocol to per protocol), and 11.9.3 (from A descriptive statistics to Descriptive statistics).

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' study vaccine/product and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine/product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
IND number	16531
EudraCT number	2017-000880-34
Date of protocol amendment	Amendment 2 Final: 27 March 2019
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 month schedule in COPD patients aged 40 to 80 years with a previous history of acute exacerbation (AECOPD).
Investigator name	_____
Signature	_____
Date	_____
PPD **name, function and title**	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 9.4.2.

5. GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 9.8.

SYNOPSIS

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 month schedule in COPD patients aged 40 to 80 years with a previous history of acute exacerbation (AECOPD).

Indication

Active immunisation for the reduction of frequency of moderate and severe acute exacerbations of COPD in patients with a previous history of AECOPD.

Rationale for the study and study design

- Rationale for the study

The purpose of this Phase IIB proof-of-concept (POC) study in moderate to very severe COPD patients (i.e. GOLD grade 2, 3 and 4) aged 40 to 80 years with a history of moderate or severe AECOPD in the previous 12 months is to evaluate whether the NTHi-Mcat vaccine can reduce the frequency of AECOPD in this population and to assess the vaccine's safety, reactogenicity and immunogenicity.

Several formulations of a vaccine containing the NTHi antigens (10 or 30 µg) either non-adjuvanted or combined with different adjuvants (aluminium [Al], adjuvant system [AS]01_E and $AS04_C$) were already evaluated in two previous Phase I clinical trials (NTHI-002 in healthy adults aged 18 - 40 years and NTHI-003 in current and former healthy smokers of 50-70 years old). The investigational vaccines were well-tolerated, with an acceptable safety and reactogenicity profile. These studies allowed the dose selection of the NTHi antigens (10 µg) and the adjuvant system ($AS01_E$) currently evaluated for the first time in moderate and severe COPD patients aged 45 - 81 years in the Phase II study NTHI-004.

The safety, reactogenicity and immunogenicity of different formulations of the NTHi-Mcat investigational vaccine have been evaluated in the Phase I study in healthy adults aged 19 - 40 years and in current and former smokers aged 50 - 70 years (study NTHI MCAT-001). Based on results obtained up to 30 days post-Dose 2 from this study, the $AS01_E$-adjuvanted formulation containing 10 µg of NTHi proteins PD and PE-PilA and 3.3 µg of UspA2 has been selected for evaluation in the current NTHI MCAT-002 study. Placebo will be used as a control. The NTHi-Mcat investigational vaccine and placebo will be given on top of standard of care to subjects in the respective study groups.

- Rationale for the study design

In the current study, moderate, severe and very severe COPD patients (i.e. GOLD grade 2, 3 and 4) with a history of AECOPD will receive 2 doses of the NTHi-Mcat investigational vaccine or placebo intramuscularly (IM) according to a 0, 2 month vaccination schedule, in addition to standard care.

Scheduled study visits, during which the effect of immunisation against NTHi and Mcat will be evaluated, will take place at pre-defined timepoints.

In addition to the scheduled study visits, ad hoc AECOPD-driven study visit(s) and/ or phone contact(s) will take place for each AECOPD occurring from first vaccination up to study conclusion:

  – An AECOPD visit will be scheduled as soon as possible after the onset of the AECOPD symptoms (maximum 96 hours after the onset of the symptoms).
  – Follow-up visit(s) and/or phone call(s) will take place to determine the end of the AECOPD.

- Rationale for the use of placebo

There is currently no established vaccine with recognised efficacy in reducing the frequency of AECOPD. Placebo (PBS) will therefore be used as a control.

Objectives

Primary

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

Secondary

- 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 the placebo control 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.

Tertiary

- 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. **(Amended 27 March 2019)**
- 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. **(Amended 27 March 2019)**
- 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.

Study design

- 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.
  - 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) at Visit 8 (Day 451) or last visit/ contact of Epoch 002.
- End of Study (EoS): Last testing results released of samples collected up to Visit 8 (Day 451).
- 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).

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
10-10-3-AS	~300	40 – 80 years	x	x
CONTROL	~300	40 – 80 years	x	x

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		10-10-3-AS	CONTROL
10-10-3/AS01E	NTHi-Mcat 10-10-3 AS01E	x	
Placebo	Formulation buffer S9b		x

- Control: Placebo control (PBS)
- Vaccination schedule: at Visit 1 (Day 1) and Visit 3 (Day 61).

- Treatment allocation: subjects will be minimised by:
  - Age (40 - 59 years or 60 - 80 years).
  - Number of moderate/ severe AECOPD in the previous year (< 2 or ≥ 2).
  - GOLD grade (GOLD 2, GOLD 3 or GOLD 4).
  - Country

  All factors will have equal weight in the minimisation algorithm.

  Subjects will be randomised using a centralised randomisation system on internet (SBIR) at first dose. Treatment number allocation (without randomisation) will also occur at Dose 2 using SBIR.

- Blinding: observer-blind.

Synopsis Table 3 Blinding of study epochs

Study Epochs	Study Groups	Blinding
Epoch 001	10-10-3-AS / CONTROL	observer-blind
Epoch 002	10-10-3-AS / CONTROL	observer-blind

- 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 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.
  - **Sputum samples** 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.

- **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).

Type of study: self-contained

- Data collection: Electronic Case Report Form (eCRF) and Electronic Diary Cards (eDiary) and Phone Contacts.
- Safety monitoring

Safety evaluations by the safety review team (SRT) (blinded) and by an internal Safety Review Committee (iSRC) (unblinded) will be performed. Refer to Section 9.10 for more detailed information on safety monitoring.

Number of subjects

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 and approximately 300 subjects receiving two doses of placebo (PBS).

Endpoints

Primary

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

Secondary

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.

Tertiary

Sputum sample PCR:

- Occurrence (presence and absence)***, acquisition, apparition,*** 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. **(Amended 27 March 2019)**

Sputum sample culture:

- Occurrence (presence and absence)***, acquisition, apparition,*** 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. **(Amended 27 March 2019)**
- 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 score 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.

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µL:	Microliter
AE:	Adverse event
AECOPD:	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
ANCOVA:	Analysis of co-variance
AS:	Adjuvant system
ATS DLD 78A:	American Thoracic Society and the Division of Lung Diseases 78A
CAT:	COPD assessment test
CD40L:	CD40 ligand
CI:	Confidence interval
CLS:	Clinical Laboratory Sciences
CMI:	Cell-mediated immunogenicity
COPD:	Chronic Obstructive Pulmonary Disease
CXCL10:	C-X-C motif chemokine 10 (= IP-10)
eCOA:	Electronic Clinical Outcome Assessment
eCRF:	Electronic Case Report Form
EGA:	Estimated gestational age
ELISA:	Enzyme-linked immunosorbent assay
EoS:	End of Study
EU/ml:	ELISA unit per millilitre
EXACT-PRO:	EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome
FAS:	Full-Analysis Set
FCV:	forced capacity vital
FDA:	Food and Drug Administration, United States

FEV1:	Forced expiratory volume in 1 second
GCP:	Good Clinical Practice
GMC:	Geometric mean concentration
GOLD:	Global initiative for Chronic Obstructive Lung Disease
GSK:	GlaxoSmithKline
HCU:	Healthcare utilisation
HRQOL:	Health-related quality of life
hsCRP:	High-sensitivity C-reactive protein
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
ICS:	Intracellular cytokine staining
IDMC:	Independent Data Monitoring Committee
IFN-γ	Interferon gamma
IgG:	Immunoglobulin G
IL:	Interleukin
IM:	Intramuscular
IND:	Investigational new drug
IP-10:	Interferon gamma-induced protein 10 (= CXCL10)
iSRC:	Internal Safety Review Committee
LLOQ:	Lower limit of quantification
LMP:	Last menstrual period
LSLV:	Last Subject Last Visit
LTOT:	Long-term oxygen therapy
Mcat:	*Moraxella catarrhalis*

mMRC:	Modified Medical Research Council Dyspnoea
NTHi:	Non-Typeable *Haemophilus influenzae*
PBMC:	Peripheral blood mononuclear cell
PBS:	Phosphate buffered saline
PC:	Phone call
PCD:	Primary completion date
PCR:	Polymerase chain reaction
PD:	Protein D
PE:	Protein E
PilA:	Type IV pilus assembly protein
pIMD:	Potential immune-mediated disease
PPS:	Per-protocol set
RNA:	Ribonucleic acid
SAE:	Serious adverse event
SBIR:	Randomisation system on internet
SGRQ-C:	St. George's Respiratory Questionnaire for COPD patients
SPM:	Study Procedures Manual
SRT:	Safety review team
TNF-α:	Tumour necrosis factor alpha
TVC:	Total vaccinated cohort
US:	United States
UspA2:	Ubiquitous surface protein A2
VE:	Vaccine efficacy

VSMB:	Vaccine Safety Monitoring Board
WHO:	World Health Organisation

GLOSSARY OF TERMS

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).*** **(Amended 27 March 2019)**
Adequate contraception:	Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example: • abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle, • Combined estrogen and progesterone oral contraceptives, • injectable progestogen, • implants of etenogestrel or levonorgestrel, • Contraceptive vaginal ring, • percutaneous contraceptive patches, • intrauterine device or intrauterine system, • male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject, The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history. • male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive Adequate contraception does not apply to subjects of child bearing potential with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.
Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory

	finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Alcoholism:	Alcoholism, also known as dependency on alcohol or alcohol addiction, is a chronic disease. The signs and symptoms of alcoholism include: • A strong craving for alcohol. • Continued use despite repeated physical, psychological, or interpersonal problems. • The inability to limit drinking.
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.*** **(Amended 27 March 2019)**
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment.
Current smoker:	A person who is currently smoking or who stopped smoking within the past 6 months before study start.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study: **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.

Epoch:	An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis.
Former smoker:	A person who stopped smoking for at least 6 months at the time of study start.
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Pack-years of smoking:	Pack-years is a quantification of cigarette smoking, a way to measure the total amount a person has smoked in the course of his/ her lifetime. The number of pack-years is calculated as follows: (average number of *cigarettes* smoked per day x number of years smoked)/ 20 E.g. a smoking history of 10 pack-years means having smoked 20 cigarettes per day for 10 years or having smoked 10 cigarettes per day for 20 years. *Note*: For the purpose of this study, pipe and/or cigar use should not be used to calculate pack-year history.
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of diseases that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.

Solicited adverse event:	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study vaccine:	Any investigational vaccine being tested and/or any authorized use of a vaccine/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine.
Study Works:	Secure electronic Clinical Outcome Assessment (eCOA) Web-Portal where reports are displayed to investigator staff showing data entered on the eCOA devices used by subjects (eDiary) and allowing the investigator staff to make decisions such as changing the eligibility status of the patient on the study.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule,…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to the treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

1. INTRODUCTION

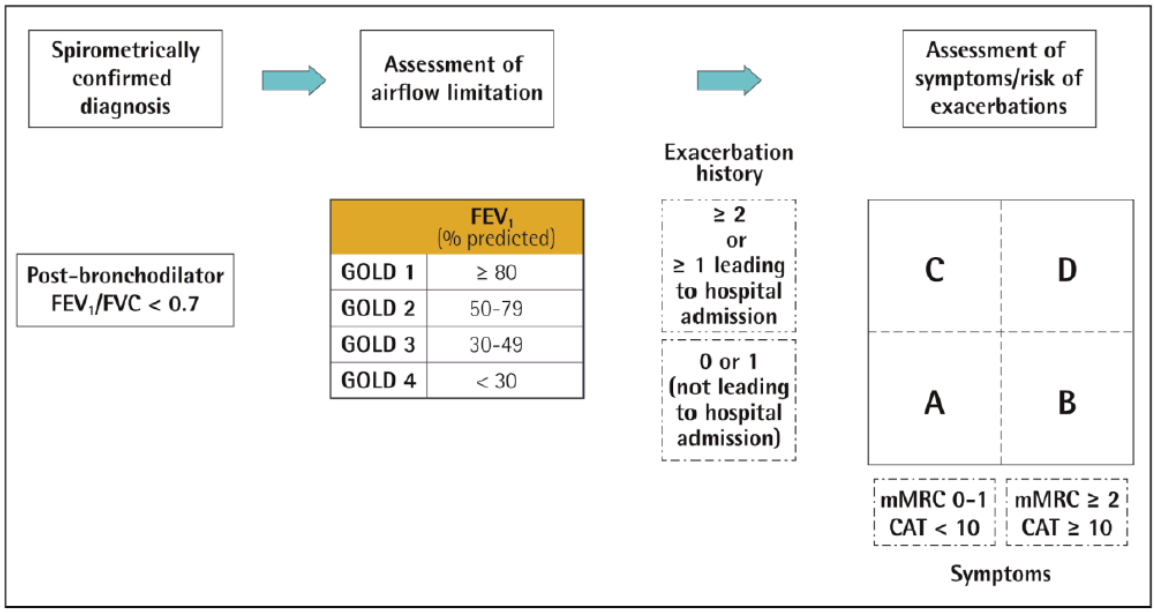
1.1. Background

1.1.1. Chronic obstructive pulmonary disease and acute exacerbations

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive in the long term. The classification of COPD severity is done based on the patient's spirometric classification according to [GOLD, 2013]. The airflow limitation in COPD patients can be classified into Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades as shown in Figure 1 [GOLD, 2017].

Additional parameters can be collected in order to allow for a combined assessment that could be used for future evaluation (Figure 1) [GOLD, 2017].

Figure 1 The refined ABCD assessment tool



COPD = Chronic Obstructive Pulmonary Disease; **GOLD** = Global Initiative for Chronic Obstructive Lung Disease; **CAT** = COPD assessment test; **mMRC** = Modified Medical Research Council Dyspnoea; **FEV_1** = Forced expiratory volume of air expired in 1 second; **FVC** = forced expiratory vital capacity.

Number of exacerbations per year, number of hospitalizations per year and CAT score will be collected at the enrollment in order to allow for the classification according to the [GOLD, 2017]:

- Patient Group A – Low Risk, Less Symptoms; and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score < 10 or Modified Medical Research Council Dyspnoea (mMRC) grade 0-1*
- Patient Group B – Low Risk, More Symptoms; and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score ≥ 10 or mMRC grade ≥ 2*

- Patient Group C – High Risk, Less Symptoms; and/or ≥ 2 exacerbations per year or ≥ 1 with hospitalization for exacerbation; and CAT score < 10 or mMRC grade 0-1*
- Patient Group D – High Risk, More Symptoms; and/or ≥ 2 exacerbations per year or ≥ 1 with hospitalization for exacerbation; and CAT score ≥ 10 or mMRC grade ≥ 2*.

* *Note:* in this study, the mMRC scaling will not be used to classify patients in different COPD categories.

The airflow limitation is associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles of gases. The most important environmental risk factor for COPD is tobacco smoking, even though other factors, such as occupational exposure, may also contribute to the development of the disease [GOLD, 2017]. It is a multi-component disease with several contributory mechanisms, including airway inflammation, airway obstruction, mucociliary dysfunction and structural changes to the airways [American Thoracic Society and European Respiratory Society, 2004; GOLD, 2017]. Together, these mechanisms manifest as an accelerated decline in lung function, with symptoms such as breathlessness on physical exertion, deteriorating health status and exacerbations.

In 2015, COPD ranked third among the global age-standardised death rates for both sexes, with about 3.2 million patients dying of the disease [Wang, 2016]. The morbidity and mortality of COPD is substantially contributed to acute exacerbation of COPD (AECOPD), which are events during which the patient's respiratory symptoms acutely worsen beyond normal day-to-day variations and which require a change in maintenance treatment. Higher exacerbation rates have been related to a faster decline in lung function and are known to have a negative effect on the patient's quality of life. Moreover, frequent exacerbations are associated with significant mortality, particularly if they require hospitalization. Between 40 - 60% of medical expenditure for COPD is a direct consequence of AECOPD [Cazzola, 2008].

Acute exacerbations and comorbidities contribute to the overall disease severity in individual COPD patients. An acute exacerbation of COPD (AECOPD) is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [GOLD, 2017]. The rate at which acute exacerbations occur varies greatly between patients, with severe patients exacerbating more often. AECOPD additionally increase morbidity and mortality, leading to faster decline in lung function, poorer functional status, and have a significant impact on healthcare systems worldwide [Sapey, 2006].

The lungs are known to be colonised with different strains of bacteria [Erb-Downward, 2011; Wilkinson, 2017]. In COPD patients, acquisition of new bacterial strains is believed to be an important cause of AECOPD [Sethi, 2002]. Although estimates vary widely, Non-Typeable *Haemophilus influenzae* (NTHi) appears to be the main bacterial pathogen associated with AECOPD (11-38%), followed by *Moraxella catarrhalis* (Mcat) (3-25%) and *Streptococcus pneumoniae* (4-9%) [Alamoudi, 2007; Bandi, 2003; Hutchinson, 2007; Ko, 2007; Larsen, 2009; Murphy, 2005; Papi, 2006; Rosell, 2005; Sethi, 2002; Sethi, 2008; Wilkinson, 2006].

Reducing the frequency and severity of AECOPD is one of the main goals of COPD maintenance treatment. The severity of AECOPD can be graded according to the intensity of medical intervention required (see Table 1) [Wedzicha, 2007].

Table 1 Classification of severity of AECOPD

Grade	Intensity of medical intervention
Mild	Can be controlled with an increase in dosage of regular medications
Moderate	Requires treatment with systemic corticosteroids and/ or antibiotics
Severe	Requires hospitalisation*

* In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment for AECOPD that would not have been appropriate in the physician's office or in an out-patient setting.

1.1.2. Current management of AECOPD

The use of antibiotics is recommended by several guidelines [American Thoracic Society and European Respiratory Society, 2004] as a standard treatment for COPD patients with AECOPD showing purulent sputum. However, as not all patients have confirmed bacterial-related exacerbations, there is an inappropriate use of antibiotics, leading to the spread of antibiotic-resistant bacteria [Daubin, 2008]. Infections with multidrug-resistant bacteria have been linked to increase in morbidity, length of hospitalisation, health care cost and mortality [Nseir, 2008].

A wide range of pharmacologic (such as inhaled corticosteroids, bronchodilators, phosphodiesterase inhibitors, theophyllines, long-term antibiotics and mucolytics) and non-pharmacologic (such as lung volume reduction surgery, home oxygen, ventilatory support and pulmonary rehabilitation) interventions also exist to reduce AECOPD and hospitalisation rates. However, a need for further novel interventions remains because current approaches are not completely effective, even when targeted and used optimally.

Prevention of AECOPD is an insufficiently addressed medical need today, despite existing preventative therapies (bronchodilators such as long-acting muscarinic antagonists [LAMA], long-acting beta agonists [LABA], methylxanthines, corticosteroids, phosphodiesterase-4 inhibitors and combination drugs), and is thought to remain so in the 10-years horizon.

There is currently no vaccine indicated for prevention of AECOPD, even though influenza and pneumococcal vaccines are routinely recommended to COPD patients. The availability of a vaccine for the prevention of bacterial AECOPD could contribute significantly to the current management of COPD, in terms of reducing the risk of bacterial exacerbations as well as the inappropriate use of antibiotics.

1.1.3. GSK Biologicals' NTHi-Mcat investigational vaccine

GlaxoSmithKline (GSK) Biologicals is developing a new NTHi-Mcat investigational vaccine against diseases caused by NTHi and Mcat. The investigational vaccine that will be evaluated in the present study is an adjuvanted multi-component vaccine consisting of surface proteins from NTHi and Mcat. The selected NTHi antigens are three conserved surface proteins presented as a free recombinant Protein D (PD) and a recombinant fusion protein combining Protein E (PE) and protein PilA, named PE-PilA. The selected Mcat antigen is UspA2, a surface protein from Mcat that is expressed in more than 95% of the Mcat strains. The vaccine is being developed for active immunisation to reduce the frequency of moderate and severe acute exacerbations of COPD in patients with a previous history of AECOPD.

The target population of the GSK NTHi-Mcat investigational vaccine are COPD patients, who are often elderly, who are known to have a weakened immune response due to functional defects and altered frequencies of innate and adaptive immune cells, with impaired generation of long-term immune memory (immunosenescence) [Weinberger, 2008]. Moreover, the immune response of COPD patients has been suggested to be disturbed both locally and systemically. Using an adjuvant may help to induce a higher and longer-lasting immune response.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies and the epidemiological information of the NTHi-Mcat investigational vaccine.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

The purpose of this Phase IIB proof-of-concept (POC) study in moderate to very severe COPD patients (i.e. GOLD grade 2, 3 and 4) aged 40 to 80 years with a history of moderate or severe AECOPD in the previous 12 months is to evaluate whether the NTHi-Mcat vaccine can reduce the frequency of AECOPD in this population and to assess the vaccine's safety, reactogenicity and immunogenicity.

Several formulations of a vaccine containing the NTHi antigens (10 or 30 µg) either non-adjuvanted or combined with different adjuvants (aluminium [Al], adjuvant system [AS]01_E and $AS04_C$) were already evaluated in two previous Phase I clinical trials (NTHI-002 in healthy adults aged 18 - 40 years and NTHI-003 in current and former healthy smokers of 50-70 years old). The investigational vaccines were well-tolerated, with an acceptable safety and reactogenicity profile. These studies allowed the dose selection of the NTHi antigens (10 µg) and the adjuvant system ($AS01_E$) currently evaluated for the first time in moderate and severe COPD patients aged 45 - 81 years in the Phase II study NTHI-004.

The safety, reactogenicity and immunogenicity of different formulations of the NTHi-Mcat investigational vaccine have been evaluated in the Phase I study in healthy adults aged 18 - 40 years and in current and former smokers aged 50 - 70 years (study NTHI MCAT-001). Based on results obtained up to 30 days post-Dose 2 from this study, the $AS01_E$-adjuvanted formulation containing 10 µg of NTHi proteins PD and PE-PilA and 3.3 µg of UspA2 has been selected for evaluation in the current NTHI MCAT-002 study. Placebo will be used as a control. The NTHi-Mcat investigational vaccine and placebo will be given on top of standard of care to subjects in the respective study groups.

1.2.2. Rationale for the study design

In the current study, moderate, severe and very severe COPD patients (i.e. GOLD grade 2, 3 and 4) with a history of AECOPD will receive 2 doses of the NTHi-Mcat investigational vaccine or placebo intramuscularly (IM) according to a 0, 2 month vaccination schedule, in addition to standard care.

1.2.2.1. Scheduled study visits and AECOPD-driven study contacts

Scheduled study visits, during which the effect of immunisation against NTHi and Mcat will be evaluated, will take place at pre-defined timepoints (see Figure 2).

In addition to the scheduled study visits, *ad hoc* **AECOPD-driven study visit(s) and/ or phone contact(s)** will take place for each AECOPD occurring from first vaccination up to study conclusion:

- An AECOPD visit will be scheduled as soon as possible after the onset of the AECOPD symptoms (maximum 96 hours after the onset of the symptoms).
- Follow-up visit(s) and/or phone call(s) will take place to determine the end of the AECOPD.

1.3. Rationale for the use of placebo

There is currently no established vaccine with recognised efficacy in reducing the frequency of AECOPD. Placebo will therefore be used as a control.

1.4. Benefit: Risk Assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of the NTHi-Mcat investigational vaccine.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.4.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
NTHi-Mcat investigational vaccine		
Theoretical risk of acquiring a vaccine-induced autoimmune disease after vaccination	No confirmed signals related to this potential risk have been identified during the preclinical and clinical programs so far	Close monitoring of potential immune-mediated diseases in clinical development programs using adjuvants systems. The potential risk for events of possible autoimmune aetiology to occur is mentioned in the Informed Consent Form (ICF).
Study Procedures		
Risk of blood sampling	Blood sampling associated risk of syncope, dizziness, infection at the site after or during venepuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health.
Risk of induced sputum sampling	Small risk of bronchoconstriction as a reaction to the inhalation of the saline solution used to induce the sputum	Sputum induction is generally considered safe. The potential risk of bronchoconstriction is mentioned in the ICF.
Spirometry	***In a few cases spirometry has been*** associated with dizziness. Strong exhalation can cause increased pressure in chest, eyes or stomach. ***Occasionally after receiving the albuterol/salmeterol inhaler, a temporary sensation of "heart racing" and shakiness may be felt.*** **(Amended 27 March 2019)**	Screening of patients with a contraindication for spirometry testing (such as recent eye surgery, recent thoracic or abdominal surgery procedures, unstable cardiovascular status, recent myocardial infection or pulmonary embolism). Risks associated with spirometry are mentioned in the ICF.

1.4.2. Benefit Assessment

Benefits considerations include:

- Contribution to the process of developing a vaccine which may help in reducing AECOPD frequency.
- Medical evaluations/assessments associated with this study (e.g. physical examination, spirometry).
- Close follow-up of COPD patients during the study.

1.4.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risks to subjects participating in this study, the potential and/or known risks identified in association with the candidate NTHi-Mcat vaccine are justified by the anticipated benefits that may be afforded to patients for the prevention of AECOPD.

2. OBJECTIVES

2.1. 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.

Refer to Section 11.1 for the definition of the primary endpoint.

2.2. 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 the placebo control 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.

Refer to Section 11.2 for the definition of the secondary endpoints.

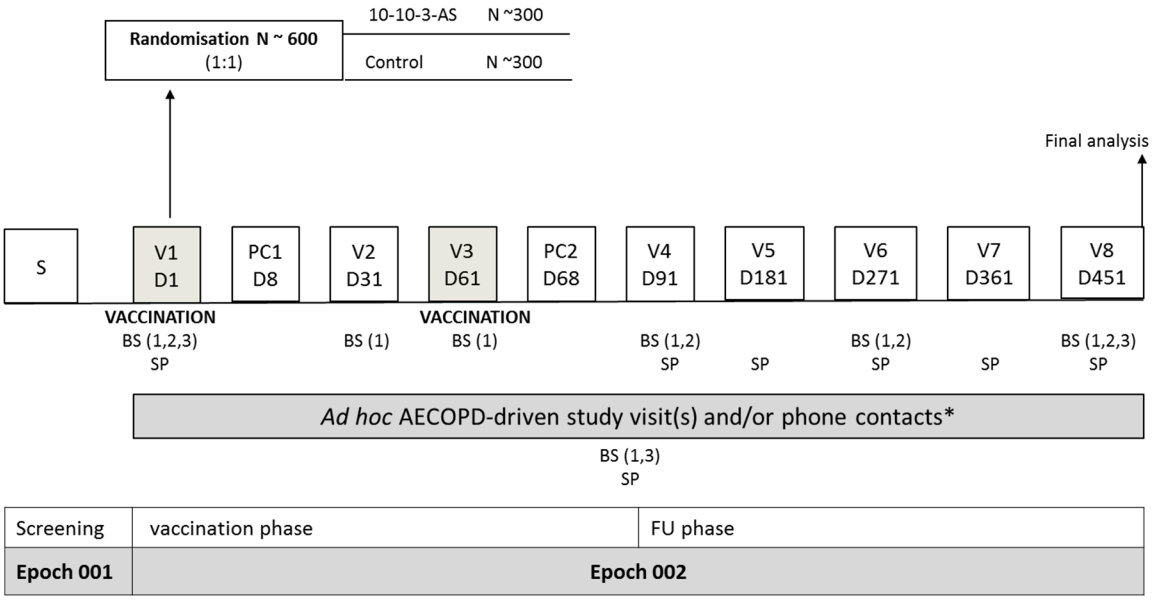
2.3. Tertiary objectives

- 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. **(Amended 27 March 2019)**
- 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. **(Amended 27 March 2019)**
- 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.

Refer to Section 11.3 for the definition of the tertiary endpoints and to section 11.12.1 for the reporting of tertiary endpoint results.

3. STUDY DESIGN OVERVIEW

Figure 2 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 need to be repeated within 7 days (see Table 6 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.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 6.5), are essential and required for study conduct.

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.
  - 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) at Visit 8 (Day 451) or last visit/contact of Epoch 002.

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected up to Visit 8 (Day 451).

Refer to glossary of terms for the definition of EoS.

- 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).

Table 2 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
10-10-3-AS	~300	40 – 80 years	x	x
CONTROL	~300	40 – 80 years	x	x

Table 3 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		10-10-3-AS	CONTROL
10-10-3/AS01E	NTHi-Mcat 10-10-3 AS01E	x	
Placebo	Formulation buffer S9b		x

- Control: placebo control (PBS).
- Vaccination schedule: at Visit 1 (Day 1) and Visit 3 (Day 61).
- Treatment allocation: subjects will be minimised by:
  - Age (40 - 59 years or 60 - 80 years).
  - Number of moderate/ severe AECOPD in the previous year (< 2 or ≥ 2).
  - GOLD grade (GOLD 2, GOLD 3 or GOLD 4).
  - Country

All factors will have equal weight in the minimisation algorithm.

Subjects will be randomised using a centralised randomisation system on internet (SBIR) at first dose. Treatment number allocation (without randomisation) will also occur at Dose 2 using SBIR.

- Blinding: observer-blind.

Table 4 Blinding of study epochs

Study Epochs	Study Groups	Blinding
Epoch 001	10-10-3-AS / CONTROL	observer-blind
Epoch 002	10-10-3-AS/ CONTROL	observer-blind

- 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 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.
  - **Sputum samples** 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.
- **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).
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF), electronic Diary Cards (eDiary) and Phone Contacts.
- Safety monitoring: Safety evaluations by the safety review team (SRT) (blinded) and by an internal Safety Review Committee (iSRC) (unblinded) will be performed.

Refer to section 9.10 for detailed description of safety monitoring.

4. AECOPD

4.1. Detection of AECOPD

Occurrence of potential AECOPD will be monitored by means of electronic Diary Cards which the subject will use to record his/ her morning symptoms on a daily basis. The electronic Diary Cards will be programmed as to detect potential AECOPD as follows (based on the Anthonisen criteria [Anthonisen, 1987]):

- Worsening of two or more of the following major symptoms for at least two consecutive days: dyspnoea, sputum volume, sputum purulence (colour), 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/99.5°F) without other cause, increased cough, increased wheeze.

Note: 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.

Each time a potential AECOPD is detected via the electronic Diary Card, the device will alert the subject to contact the study site, and at the same time an alert will be sent to the site so that the investigator contacts the subject to determine if the alert is an AECOPD or not, and if an AECOPD visit is warranted. Delegation of this responsibility from the investigator to study staff should be agreed with the Sponsor. In addition, the site should proactively follow-up all data received via the electronic Diary Card and contact the subject whenever deemed necessary.

During the contact with the subject, the investigator will determine whether the subject might actually be experiencing an AECOPD (e.g. notifications that can be explained solely by increased physical activity will not be considered):

- If the investigator concludes that the subject is not experiencing an AECOPD, this should be documented/ reported in the Study Works (Web portal). Please refer to study procedures manual (SPM) for more details on how to perform this.
- If the investigator concludes that the subject is experiencing an AECOPD, an occurrence of AECOPD will be entered in the eCRF and an AECOPD visit will be scheduled as soon as possible after the onset of AECOPD symptoms as recorded in the electronic Diary Card or confirmed by the subject (maximum 96 hours after onset of symptoms and, if applicable, preferably before starting treatment with antibiotics). The AECOPD onset date will be captured in the eCRF and additional information about severity will be also collected.
  - In case the AECOPD is confirmed but no AECOPD visit can take place, the site should record the information in the medical records subject files, and in the eCRF in medical records section and obtain all relevant information regarding the AECOPD (hospital record, medical record etc) and record this in the eCRF.

- If the investigator concludes the subject is experiencing/continuing with the same event for which a visit has been performed already, an AECOPD visit should not take place. Medical treatment should be foreseen according to standard medical practice outside of the study.

During the AECOPD visit, the investigator will again confirm the occurrence of the AECOPD based on clinical and medical judgement and based on the Anthonisen criteria and will record its date of onset. The end date of the AECOPD and its severity will be determined/ confirmed by the investigator during (a) follow up phone call(s), which will take place at least every 2 weeks until the AECOPD has resolved.

If an AECOPD occurs at the time when one of the scheduled [stable] study visits is planned, it should be handled and recorded as an AECOPD visit, with all relevant AECOPD visit study procedures performed and, if possible, the stable study visit should be re-scheduled to a later date, when the subject is stable again and within the time window specified in the protocol.

The site must engage their best efforts to reach the patients, however, if the site does not succeed in contacting the patient, the reason should be recorded and an explanation given about what occurred. For example, the subject could be hospitalized or could visit a different physician (and in that case medical record***s*** should be obtained), or the subject is on holidays or not able to go ***to*** the site.

For the analysis of the primary endpoint, the AECOPD must be confirmed by the investigator:

- Via a phone call following the eDiary alert, and/or
- At a spontaneous site visit with or without eDiary alert and/or
- At the AECOPD visit and/or
- Via medical records

If an AECOPD occurs at the time of a scheduled study visit, it should be handled and recorded as an AECOPD visit, with all relevant study procedures done during AECOPD-driven study visits performed and, if possible, the scheduled visit should be re-scheduled to a later date within the time window specified in the protocol.

Some subjects may have been supplied with a prescription for antibiotics and/or steroids for treatment of AECOPD to use according to instructions provided by their physician in the event of an AECOPD occurring at a future date. During the course of this study, following an eDiary alert for potential AECOPD or other contact for potential AECOPD, the investigator should make all possible efforts to ensure contact with the patient prior to the patient self-administering any antibiotics or steroids for their potential AECOPD. To manage situations where this prior contact cannot occur the investigator should use their clinical judgement.

Please refer to the SPM for more details on detection and recording of AECOPDs.

4.1.1. Date of onset and end date of AECOPD

Per inclusion criteria, the subject should be a stable COPD patient (i.e. a subject for whom the last episode of AECOPD is resolved for at least 30 days at the time of ***first vaccination***). **(Amended 27 March 2019)** This effectively sets the baseline for evaluating the symptoms stated within the Anthonisen criteria (see Section 4.1). The date of onset of AECOPD is the first day (of at least 2 consecutive days) of worsening symptoms of COPD as determined by the investigator according to the Anthonisen criteria. For example, worsening of dyspnoea, sputum volume and sputum purulence is evaluated daily by the patient relative to this baseline. For an AECOPD confirmed by the investigator following an eDiary alert the onset date is considered to be the first day of 2 consecutive days that the patient enters symptoms meeting the Anthonisen criteria. Each day that there is no new symptom effectively becomes the new baseline. Once the Anthonisen criteria are met, an ***eDiary*** alert is triggered. **(Amended 27 March 2019)** If the investigator determines this to be an AECOPD, that event is recorded via the eCRF. Subsequently, the investigator will follow the patient via phone contact (or clinic visit) at least every 2 weeks until resolution of this event.

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 should be given to symptoms recorded in the electronic Diary Card and during the phone calls and/or study subject evaluation.

The patient continues to daily monitor the symptoms within the Anthonisen criteria relative to the symptom state at the time of determined resolution.

Both start and end date of each confirmed AECOPD occurring from Visit 1 to study conclusion will be recorded in the eCRF.

4.1.2. Guideline for assessing AECOPD that increase in severity

If an exacerbation starts off as mild, but becomes moderate or severe, or starts off as moderate and becomes severe, the exacerbation should be captured as one exacerbation and classified by its highest level of severity.

4.2. Treatment of AECOPD

AECOPD should be treated according to standard of care.

5. STUDY COHORT

5.1. Number of subjects

The target is to enrol approximately 300 eligible COPD patients aged 40 to 80 years per study group (i.e. ~600 subjects in total). Refer to Section 11.4 for a detailed description of the criteria used in the estimation of the sample size.

Approximately 20% of the subjects (~120 subjects in total) will be part of a **sub-cohort for CMI** analysis. An additional blood sample will be taken from these subjects at specified timepoints (Visit 1, 4, 6 and 8). The CMI sub-cohort will be selected from sites able to process the blood samples according to GSK procedures for peripheral blood mononuclear cell (PBMC) preparation.

Table 5 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
Sub-cohort for CMI	At specific timepoints (Visit 1, 4, 6 and 8), an additional blood sample will be taken from these subjects for evaluation of the vaccine component-specific CMI responses.	~ 120 subjects (~ 60 subjects in each group)

5.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. electronic Diary Card completion, number of blood draws, sputum sampling, pre- and post-bronchodilator spirometry, return for follow-up visits).
- Written informed consent obtained from the subject prior to performing any study specific procedure.
- A male or female between, and including, 40 and 80 years of age at the time of the first vaccination.
- Confirmed diagnosis of COPD (based on post-bronchodilator spirometry) with forced expiratory volume in 1 second (FEV1) over forced vital capacity (FVC) ratio (FEV1/FVC) < 0.7, AND FEV1 < 80% predicted (GOLD 2, 3 and 4).
- Current or former smoker with a cigarette smoking history of ≥ 10 pack-years.

  Refer to the glossary of terms for the definitions of pack-years and of current and former smoker.

- Stable COPD patient* with documented history** (e.g. medical record verification) of at least 1 moderate or severe AECOPD within the 12 months before Screening.

  * Patient for whom the last episode of AECOPD is resolved for at least 30 days at the time of first vaccination.

  ** A documented history of a COPD exacerbation (e.g. medical record verification) is a medical record of worsening COPD symptoms that required systemic/oral corticosteroids and/or antibiotics (for a moderate exacerbation) or hospitalization (for a severe exacerbation). Prior use of antibiotics alone does not qualify as an exacerbation history unless the use was associated with treatment of worsening symptoms of COPD, such as increased dyspnea, sputum volume, or sputum purulence (color). Subject verbal reports are not acceptable.

  Refer to the Study Procedures Manual (SPM) for additional details on what is accepted as documented history of AECOPD. Refer to Table 1 for the definitions of moderate and severe AECOPD.

- Capable of complying with the daily electronic Diary Card completion throughout the study period, according to investigator's judgement at Visit 1.

  Refer to the SPM for recommendations on what is considered adequate compliance by Visit 1.

- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause.

  Please refer to the glossary of terms for the definition of menarche and menopause.

- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination, and
  - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

  Please refer to the glossary of terms for the definition of adequate contraception.

5.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the study period.

- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Administration of immunoglobulins or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Planned administration/ administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of vaccine, with the exception of any influenza or pneumococcal vaccine which may be administered ≥15 days preceding or following any study vaccine dose.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine dose (e.g. methotrexate).
- Administration of systemic corticosteroids (prednisone ≥10 mg/day, or equivalent) within the 30 days before first vaccination.
  - Subjects who received systemic corticosteroids within this period may be enrolled at a later date if enrolment is still open.
  - Inhaled and topical steroids are allowed.
- Administration of systemic antibiotics within the 30 days before first vaccination.
  - Subjects who received systemic antibiotics within this period may be enrolled at a later date if enrolment is still open.
- Chronic use of antibiotics for prevention of AECOPD (e.g. azithromycin).
- Acute disease and/or fever at the time of first vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Oxygen therapy: Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min (Oxygen use ≤3L/min flow is not exclusionary).
- Planned lung transplantation.
- Lung resection: Subjects with planned lung volume reduction surgery during the study or within the 12 months prior to first vaccination.
- Diagnosis of α-1 antitrypsin deficiency as the underlying cause of COPD.

- Diagnosed with a respiratory disorder other than COPD at time of enrolment (such as sarcoidosis, active tuberculosis, clinically significant bronchiectasis, clinically significant lung fibrosis, clinically significant pulmonary embolism, clinically significant pneumothorax, current diagnosis of asthma in the opinion of the investigator), or chest X-ray/ CT scan revealing evidence of clinically significant abnormalities not believed to be due to the presence of COPD. Subjects with allergic rhinitis do not need to be excluded and may be enrolled at the discretion of the investigator.
- History of immune-mediated disease other than COPD.

  Please refer to Table 19 for a non-exhaustive List of potential immune-mediated diseases. If the subject has any condition on this list, they must be excluded unless the aetiology is clearly documented to be non-immune mediated.

  The investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin and thus meet the exclusion criteria.
- Previous vaccination with any vaccine containing NTHi and/ or Mcat antigens.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines and/ or the bronchodilator used for spirometry assessment during the study.
- Contraindication for spirometry testing (such as recent eye surgery, recent thoracic or abdominal surgery procedures, unstable cardiovascular status, recent myocardial infarction or pulmonary embolism).
- Unstable or life threatening cardiac disease: subjects with any of the following at Screening (Visit 1) would be excluded:
  - Myocardial infarction or unstable angina in the last 6 months.
  - Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months
  - NYHA Class IV Heart failure
- Malignancies within the previous 5 years (excluding non-melanotic skin cancer and carcinoma in situ of the cervix, if considered cured) or lymphoproliferative disorder.
- Any known disease or condition likely to cause death during the study period.
- Pregnant or lactating female.
- Current alcoholism and/or drug abuse.

  Refer to the glossary of terms for the definition of alcoholism.
- Other condition which the investigator judges may put the safety of the subject at risk through study participation or which may interfere with the study findings (e.g. anaemia, patient on dialysis).
- Planned move to a location that will complicate participation in the trial through study end.

6. CONDUCT OF THE STUDY

6.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for GCP, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

6.2. Subject identification and randomisation

6.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.

6.2.2. Randomisation of treatment

6.2.2.1. Randomisation of supplies

The randomisation of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centres /warehouse(s).

6.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

6.2.2.2.1. Study group and treatment number allocation

The target will be to enrol approximately 600 eligible subjects who will be randomly assigned to two study groups in a (1:1) ratio (approximately 300 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for age (40 - 59 years or 60 - 80 years), number of moderate/ severe AECOPD in the previous year (< 2 or ≥2**),** GOLD grade (GOLD 2, GOLD 3 or GOLD 4) and country. Minimisation factors will have equal weight in the minimisation algorithm**.**

Details on the minimisation algorithm are reported in the statistical analysis plan.

At Visit 1, before administration of vaccine Dose 1 to eligible subjects who signed and dated the ICF at the Screening Visit, the study staff in charge of the vaccine administration will access SBIR. Upon providing the subject's age category (40 - 59 years or 60 - 80 years), number of moderate/ severe AECOPD in the previous year, his/ her GOLD grade and subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for the first dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

6.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration form/screen.

When SBIR is not available, refer to the SBIR user guide or the SPM for specific instructions.

6.2.3. Allocation of subjects to assay subsets

Approximately 50% of the subjects (~150 subjects per group) will have their sputum samples analysed for microbiology in investigator institutions or GSK designated lab. The sub-set will be selected for sites that have microbiology accredited local/hospital laboratories able to process and test the sputum samples according to GSK agreed procedures.

Sputum samples (or a subset of them), not tested for microbiology at investigator institutions or GSK designated labs, will also be used for cytokine measurement (see also Table 12).

6.3. Method of blinding

As the investigational NTHi-Mcat vaccine in this study is of different appearance than the placebo and the investigational NTHi-Mcat vaccine will have to be reconstituted whereas the placebo does not, double-blinding is not feasible.

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity and efficacy) will all be unaware of whether vaccine or placebo was administered.

Study site

Each study site is responsible for having a blinding plan. To work in an observer-blind manner, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays. Two teams of study personnel will hence be set up:

- A team of unblinded personnel (responsible for the preparation and the administration of the vaccines)
- A team of blinded personnel (responsible for the clinical evaluation of the subjects).

Refer to the SPM for guidance on vaccine preparation and administration while maintaining the blind.

Laboratory testing

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

6.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

Subjects will continue to receive their COPD standard of care during the entire study duration.

6.5. Outline of study procedures

Table 6 List of study procedures

Epoch	Epoch 001	Epoch 002									
Type of contact	Screening Visit [a]	Visit 1	Phone contact 1 [k]	Visit 2	Visit 3	Phone contact 2 [k]	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Timepoint	pre-Day 1	Day 1	Day 8	Day 31	Day 61	Day 68	Day 91	Day 181	Day 271	Day 361	Day 451
Sampling timepoint	Screening	Pre-Vacc 1	Post-Vacc 1		Pre-Vacc 2	Post-Vacc 2					
Informed consent	●										
Check inclusion/exclusion criteria	●	O									
Record of moderate and severe AECOPD within the previous year	O	●									
Check subject's COPD status		●	●	●	●	●	●	●	●	●	●
Record demographic data	●										
Record medical history, including significant comorbidities	O	●									
Vaccination history	O	●									
Smoking exposure history (ATS-DLD-78A questionnaire)	x										
Smoking status	●								●		●
Physical examination	●	O		O	O		O	O	O	O	O
Measure/record height and weight	●								O		●
Pre- and post-bronchodilator spirometry *(l)*	x [b]								x		x
Chest X-ray [d]	● [b]										
Pregnancy test [c]	● [b]	●			●						
Blood sampling:											
For humoral immunogenicity (~20 ml of blood)		●		●	●		●		●		●
For CMI (~40 ml of blood) [e]		●					●		●		●
For biomarkers, serum and plasma (~13 ml of blood)		●									●
For biomarker, haematology profile (~2 ml of blood)		●									
Sputum sampling [f]		●					●	●	●	●	●
Check contraindications to vaccination		O			O [g]						
Record pre-vaccination body temperature		●			●						
Study group and Treatment number allocation with randomisation		●			●						
Vaccination		●			●						

Epoch	Epoch 001	Epoch 002									
Type of contact	**Screening Visit** [a]	**Visit 1**	**Phone contact 1** [k]	**Visit 2**	**Visit 3**	**Phone contact 2** [k]	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Timepoint	**pre-Day 1**	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**	**Day 181**	**Day 271**	**Day 361**	**Day 451**
Sampling timepoint	**Screening**	**Pre-Vacc 1**	**Post-Vacc 1**		**Pre-Vacc 2**	**Post-Vacc 2**					
Train subject on the use of electronic Diary Card and assign electronic Diary Card to subject	O										
Distribute electronic Diary Card for recording of ***local and general*** AEs, medication and vaccination, morning and evening ***COPD*** symptoms	O										
Collection of electronic Diary Card data [h]		x	x	x	x	x	x	x	x	x	x
Distribution of Subject Card	O										
Record AEs [i]		●	●	●	●	●	●	●	●	●	●
Record SAEs [i]	●[b]	●	●	●	●	●	●	●	●	●	●
Record pregnancies [i]		●	●	●	●	●	●	●	●	●	●
Record pIMDs [i]		●	●	●	●	●	●	●	●	●	●
Record concomitant medication/products and vaccination	O	●	●	●	●	●	●	●	●	●	●
Record intercurrent medical conditions			●	●	●	●	●	●	●	●	●
Return electronic Diary Card	O [j]	O [j]									O
HRQOL questionnaires:											
CAT	x								x		x
SGRQ-C	x								x		x
Healthcare Resource Utilisation		●	●	●	●	●	●	●	●	●	●
Screening conclusion	●										
Study Conclusion											●

D = Day; **Vacc** = vaccination. **PC** = Phone contact; **CAT** = COPD assessment test; **SGRQ-C** = St. George's Respiratory Questionnaire for COPD patients; **AECOPD** = Acute exacerbation of chronic obstructive pulmonary disease; **COPD** = chronic obstructive pulmonary disease; **CMI** = cell-mediated immunity; **AE** = adverse event; **SAE** = serious adverse event; **pIMDs** = potential immune mediated diseases; **HRQOL** = health-related quality of life.

● is used to indicate a study procedure that requires documentation in the individual eCRF; O is used to indicate a study procedure that does not require documentation in the individual eCRF; x is used to indicate a study procedure that does not require documentation in the individual eCRF as the data will be directly transferred from the provider to GSK.

[a] If needed, the Screening Visit(s) can be done in more than 1 day. All screening procedures with exception of eDiary training should be performed within 7 days from 1st screening visit. The allowed maximum interval between 1st Screening Visit and Visit 1 is 29 days. If a delay occurs for an eligible subject so that interval exceeds 29 days, some study procedures performed during Screening Visit(s) need to be repeated (see footnote b). In case of AECOPD occurring before Visit 1, subjects should be treated outside the study according to standard practice. These subjects are considered screening failures. They will need to sign a new ICF, will receive a new subject number and will need to repeat the

entire Screening Visit after they are stable for at least 30 days. The entire Screening Visit can only be repeated once. Once subject is determined as eligible, the eDiary for completion will be given to the subject for a training period of maximum 14 days before Visit 1 (see Section 6.9.22.)

[b] Procedures indicated by this footnote need to be repeated if the subject has any medical condition (e.g. fever) that prevents his/her participation in the study within 29 days of Screening Visit. In that case, a re-Screening Visit must be scheduled as soon as possible and no more than 7 days from Day 29 (Day 30 - Day 36) during which the procedures indicated by this footnote need to be repeated. Same as for the initial screening, the chest X-ray only has to be redone if no chest X-ray/ CT scan is available within the last 3 months. Data obtained during re-screening procedures should be entered in the eCRF.

[c] Pregnancy tests will be performed on ***all*** females of childbearing potential ***at screening and prior to vaccination (Visit 1 and Visit 3 [(including those female subjects of childbearing potential who did not have a pregnancy test at screening because an X-ray/ CT scan was available within the last 3 months]). I***n case a chest X-ray will be performed (i.e. in subjects who do not have an X-ray / CT scan***)*** the pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive ***pregnancy*** test the chest X-ray should not be performed and the subject will be deemed not eligible for the study. Please also refer to Section 10.2.2. **(Amended 27 March 2019)**

[d] Only if no chest X-ray/ CT scan available within the last 3 months.

[e] Only for subjects in the sub-cohort for CMI.

[f] Only if, in the opinion of the investigator, it is safe for the subject. Sputum samples can be either spontaneous or induced, as per investigator judgement.

[g] Refer to Section 7.5 for more details on study procedures for subjects meeting contraindications to subsequent vaccination before administration of vaccine Dose 2.

[h] The following information will be collected with the electronic Diary Card: COPD morning and evening symptoms (including EXACT-PRO questionnaire), smoking exposure history, local and general solicited AEs and Healthcare utilisation.

[i] Please refer to Table 20 for recording periods of local and general solicited AEs, AEs/SAEs leading to study withdrawal, SAEs, pregnancies and pIMDs. Solicited AEs will be collected up to Day 7 post- vaccination. Solicited AEs ongoing at Day 7 will be followed up until resolution (for a maximum of 30 Days). Unsolicited AEs will be collected for 30 days after each vaccination and thereafter only AEs leading to Withdrawal.

[j] Only for Screening failures.

[k] The safety phone call at Day 8 and Day 68 can be performed by the (sub)-investigator or a medically trained delegate.

[l] If a good quality spirometry was not obtained, the spirometry can be repeated within 7 days, as per investigator medical judgement.

6.6. List of study procedures during AECOPD-driven study visits and phone contacts

In addition to the scheduled study visits, *ad hoc* AECOPD-driven study contacts will take place for each AECOPD occurring from first vaccination up to study conclusion. The procedures to be performed during these contacts are listed in Table 7.

In case of AECOPD occurring before Visit 1, subjects should be treated outside the study according to standard practice. These subjects are considered screening failures. They will need to sign a new ICF, will receive a new subject number and will need to repeat the entire Screening Visit after they are stable for at least 30 days.

Table 7 List of study procedures during AECOPD-driven study visits and phone contacts

Type of contact	AECOPD visit	End of AECOPD contact(s) (phone call[s] [7] and/ or visit[s])
Timepoint	**within 96 hours of onset symptoms**	**at least every 2 weeks from the AECOPD visit until AECOPD has resolved [1]**
Sampling timepoint	**AECOPD**	
Record date of visit	●	
Physical examination	O	O [2]
Chest X-ray [3]	●	
Pregnancy test [4]	●	
Confirm AECOPD and record its start date	●	
Blood sampling:		
For humoral immunogenicity (~5 ml of blood)	●	
For biomarkers, serum and plasma (~13 ml of blood)	●	
Sputum sampling [5]	●	
HRQOL questionnaire:		
CAT	x	
SGRQ-C	x	
Healthcare Resource Utilisation [8]	●	●
Record AEs [6]	●	●
Record SAEs [6]	●	●
Record pregnancies [6]	●	●
Record pIMDs [6]	●	●
Record concomitant medication/products and vaccination	●	●
Record intercurrent medical conditions	●	●
Record AECOPD severity	O	●
Record AECOPD end date		●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
x is used to indicate a study procedure that does not require documentation in the individual eCRF as the data will be directly transferred from the provider to GSK.
AECOPD = Acute exacerbation of chronic obstructive pulmonary disease; **HRQOL** = health-related quality of life; **CAT** = COPD assessment test; **SGRQ-C** = St. George's Respiratory Questionnaire for COPD patients; **AEs** = adverse events; **SAEs** = serious adverse events; **pIMDs** = potential immune mediated diseases.
[1] End of AECOPD phone calls/ visits should be scheduled at least every 2 weeks, until the AECOPD has resolved. Only the contact during which the end date of the AECOPD can be determined will be recorded in the eCRF as the end of the AECOPD contact. All intermediate contacts should be recorded on source documentation.
[2] Only applicable if the contact is a visit (not for phone calls).

[3] Only if clinically indicated to exclude another cause of worsening of symptoms (e.g. pneumonia).

[4] Pregnancy test will be performed on females of childbearing potential at each visit where a chest X-ray is performed. The pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive ***pregnancy*** test the chest X-ray should not be performed and the subject must not receive further study vaccinations. Please also refer to Section 10.2.2.

[5] Only if, in the opinion of the investigator, it is safe for the subject. Sputum samples can be either spontaneous or induced, as per investigator judgement. Self-collection of the sputum sample will be allowed in specific cases, where the first dose of antibiotics absolutely needs to be taken before an AECOPD visit can take place. As much as possible, the sputum sample collection should happen during the visit at investigator site. Self-collection is not allowed at scheduled visits when the subject should be in stable condition. See Section 6.9.15.2.

[6] Please refer to Table 20 for recording periods of local and general solicited AEs, unsolicited AEs, AEs/SAEs leading to study withdrawal, SAEs, pregnancies and pIMDs.

[7] The phone call to determine the end of AECOPD contact should be performed by the (sub)-investigator. Delegation to study staff should be agreed with the Sponsor.

[8] The AECOPD visit does not need to be recorded as a Healthcare Resource Utilisation.

6.7. Concurrence of AECOPD-driven study visits and scheduled study visits

If an AECOPD occurs at the time of a scheduled study visit, it should be handled and recorded **as an AECOPD visit**, with all relevant study procedures done during AECOPD-driven study visits performed and, if possible, the scheduled visit should be re-scheduled to a later date within the time window specified in the protocol.

If the end of AECOPD contact occurs around the same time of a scheduled study visit, they can be combined into a single visit with the study procedures relevant to both visit types performed. In this case, both visit types will need to be recorded in the eCRF separately.

Please refer to ***SPM*** for specific instructions. **(Amended 27 March 2019)**

6.8. Intervals between study visits

Whenever possible, the investigator should arrange study visits within the interval described in Table 8.

Table 8 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Scheduled study visits		
Screening Visit* → Visit 1	***14 days***	***6*** - 29 days
Visit 1 → Phone contact 1	7 days	7 - 9 days
Visit 1 → Visit 2	30 days	30 - 45 days
Visit 1 → Visit 3	60 days	60 - 75 days [1]
Visit 3 → Phone contact 2	7 days	7 - 9 days
Visit 3 → Visit 4	30 days	30 - 45 days [1]
Visit 4 → Visit 5	90 days	90 - 120 days
Visit 4 → Visit 6	180 days	180 - 210 days
Visit 4 → Visit 7	270 days	270 - 300 days
Visit 4 → Visit 8	360 days	360 - 390 days
AECOPD-driven study visit(s) and/ or phone contacts		
Onset of AECOPD symptoms as recorded in the electronic Diary Card or confirmed by the subject → AECOPD Visit	NA	max 96 hours [2]
Interval between AECOPD Visit and scheduled study visit		
AECOPD visit → scheduled study visit	NA	min 7 days [3]

PC = phone contact; **AECOPD** = Acute exacerbation of chronic obstructive pulmonary disease; **NA** = Not applicable

[1] Subjects will not be eligible for inclusion in the Per Protocol Set for analysis of immunogenicity if they make the study visit outside this interval.

[2] AECOPD visits will be scheduled as soon as possible after the onset of AECOPD symptoms as recorded in the electronic Diary Card or confirmed by the subject (maximum 96 hours after and, if applicable, preferably before starting treatment with antibiotics).

[3] If an AECOPD occurs at the time of a scheduled study visit, it should be handled and recorded as an AECOPD visit, with all relevant study procedures done during AECOPD-driven study visits performed and, if possible, the scheduled visit should be re-scheduled to a later date within the time window specified in the protocol.

* In case of a re-Screening Visit, the visit must be scheduled as soon as possible and no more than 7 days from Day 29 (Day 30 - Day 36).

6.9. Detailed description of study procedures

6.9.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. Refer to Section 6.1 for the requirements on how to obtain informed consent, as appropriate.

6.9.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 5.2 and 5.3 before enrolment.

6.9.3. Record history of moderate and severe AECOPD within the previous year

Obtain the subject's history of moderate and severe AECOPD within the previous year.

At Screening, subjects need documentation for at least 1 moderate or severe AECOPD within the previous year to be eligible for study participation.

At Visit 1, both documented (by medical record review) and self-reported, non-documented moderate and severe AECOPD within the year before Visit 1 should be recorded in the eCRF. The total number of moderate and severe AECOPD (including self-reported, non-documented AECOPD) will be entered in SBIR for randomisation.

Refer to the SPM for details on recording of moderate and severe AECOPD within the previous year.

6.9.4. Check subject's COPD status

Record the subject's COPD status (stable/ recovered or not recovered) in the eCRF.

6.9.5. Collect demographic data

Record demographic data such as year of birth, sex, race and ethnicity in the subjects' eCRF.

Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez-Losada, 2009; Kollmann, 2013], have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g. genetics, metabolism, elimination), extrinsic factors (e.g. diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both race and ethnicity will be collected for all subjects participating in the NTHI MCAT-002 study.

6.9.6. Record medical history, including significant co-morbidities

Obtain the subject's medical history by interview and/ or review of the subject's medical records and record any pre-existing conditions, signs and/ or symptoms present in a subject and significant COPD co-morbidities prior to the first study vaccination in the eCRF.

Significant comorbidities include weight loss, cardiovascular disease, hypertension, gastro-oesophageal reflux disease, osteoporosis/ osteopenia, skeletal muscle wasting and dysfunction, anxiety/ depression and diabetes.

6.9.7. Vaccination history

Record in the eCRF whether the subject received any influenza vaccination within the previous 12 months or has ever received any pneumococcal vaccination (including date of vaccination [as detailed as possible]).

6.9.8. Smoking exposure history

The subject should self-complete the smoking history questionnaire (a shortened version of the ATS-DLD-78A questionnaire), which will be provided electronically via the eDiary. The subject will have to provide information about his/ her smoking history, including duration (number of years) and number of cigarettes smoked.

From the information obtained via the questionnaire, calculation of the pack-years will be done.

The data will be directly transferred from the provider to GSK Biologicals.

Refer to the SPM for details and guidance on the smoking exposure history questionnaire.

6.9.9. Smoking status

Record the subject's smoking status (current or former smoker) in the eCRF. Refer to the glossary of terms for the definitions of current and former smoker.

6.9.10. Physical examination

At Screening, perform a complete physical examination of the subject, including vital signs after at least 10 minutes of rest (systolic/ diastolic blood pressure, heart rate, respiratory rate). Record collected information in the eCRF.

Physical examination at each study visit subsequent to the Screening Visit will be performed only if deemed necessary by the investigator or delegate.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Treatment of any abnormality observed during a physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

6.9.11. Measure/ record height and weight

Measure height and weight of the subject and record the data in the 'Physical examination' section of the eCRF.

6.9.12. Pre- and post-bronchodilator spirometry

Pre- and post-bronchodilator spirometry should be performed during specified study visits as detailed in Table 6.

Only certified study staff can perform spirometry assessment.

Spirometry will be performed following the eResearchTechnology (ERT) instructions for use FlowScreen manual and following all safety requirements.

A good quality spirometry should be obtained and will be confirmed by the spirometry provider. If a good quality spirometry was not obtained, the spirometry can be repeated within 7 days, as per investigator medical judgement. The data will be directly transferred from the provider to GSK Biologicals.

Treatment of any abnormality observed during spirometry has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

6.9.13. Chest X-ray

Screening

A posterior to anterior (PA) chest X-ray must be performed at Screening if no chest X-ray/ CT scan is available within the last 3 months.

Subjects with evidence of clinically significant abnormalities not believed to be due to the presence of COPD will not be eligible for study participation.

The pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive test, the chest X-ray should not be performed and the subject will be deemed not eligible for the study. Please also refer to section 10.2.2.

AECOPD visit

A chest X-ray should be performed at the AECOPD visit if it is clinically indicated to exclude another cause of worsening of symptoms (e.g. pneumonia).

All cases of pneumonia (including all signs and symptoms assessed to confirm pneumonia) should be documented in the eCRF.

The pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive test, the chest X-ray should not be performed and the subject must not receive further study vaccinations. Please also refer to section 10.2.2.

6.9.14. Pregnancy test

Female subjects of childbearing potential are to have a pregnancy test at Screening ***and prior to vaccination (Visit 1 and Visit 3)***. The study vaccine may only be administered if the pregnancy test is negative. **(Amended 27 March 2019)**

Note: the pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

The pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive test at time of Screening, the chest X-ray should not be performed and the subject will be deemed not eligible for the study. If the positive test occurs during the study, the subject must not receive further study vaccinations. Please also refer to section 10.2.2.

6.9.15. Sampling

Refer to the Module on Biospecimen Management in the SPM and to the central laboratory manual for detailed instructions for the collection, handling and processing of the samples.

6.9.15.1. Blood samples

Blood samples will be taken during specified study visits (scheduled visits and AECOPD visits) as detailed in Table 6 and Table 7.

Blood samples for humoral immunogenicity

A volume of approximately 20 mL of whole blood should be drawn from all subjects at Visit 1, Visit 2, Visit 3, Visit 4, Visit 6 and Visit 8. A volume of approximately 5 mL of whole blood should be drawn from all subjects at each AECOPD visit from first vaccination to study conclusion. After whole blood processing into serum, serum samples should be kept at ≤-20°C/-4°F or any temperature below until shipment.

Blood samples for CMI

A volume of approximately 40 mL of whole blood should be drawn from the subjects included in the sub-cohort for CMI at Visit 1, Visit 4, Visit 6 and Visit 8. The samples should be kept at room temperature and should be shipped as soon as possible (maximum 8 hours after whole blood collection), so that samples can be processed at the CMI laboratory within 24 hours of collection. Refer to the SPM and Central Laboratory manual for more details on sample storage conditions.

Blood samples for biomarkers

At Visit 1, Visit 8 and at each AECOPD visit from first vaccination to study conclusion: a volume of approximately 13 mL of whole blood should be drawn from all subjects and will be split and processed as follows:

- Specific biomarkers will include serum hsCRP, CXCL10 (IP-10) and plasma fibrinogen, may include other biomarkers based on results of ongoing disease understanding research.
  - Approximately 8.5 mL of whole blood will be collected and processed to serum for hsCRP & CXCL10 (IP-10) assessment. After processing, these samples should be kept at -70/-80°C until shipment.

  - Approximately 4.5 mL of whole blood (Na Citrate) will be collected and processed to plasma for fibrinogen assessment. After processing, these samples should be kept at -70/-80°C until shipment.

In addition to the above, the following will be collected at Visit 1:

- Haematology profile, including differential cell counts.
  - Approximately 2.0 mL of whole blood will be collected for haematology assessment. These samples should be kept at room temperature and shipped for testing on the day of collection, ambient.

Refer to the SPM and Central Laboratory manual for details on blood sample handling.

6.9.15.2. Sputum samples

Sputum samples will be collected during specified study visits (scheduled visits and AECOPD visits) as detailed in Table 6 and Table 7, if, in the opinion of the investigator, it is safe for the subject.

- Sputum samples can be either spontaneous or induced, as per investigator judgement. Internal standard operating procedures should be put in place to ensure proper sputum collection, sample tracking and subject safety at study collection site.
- Sputum sample collected at subject's home (spontaneous): Self-collection of the sputum sample will be allowed in specific cases, where the first dose of antibiotics absolutely needs to be taken before an AECOPD visit can take place. As much as possible, the sputum sample collection should happen during the visit at investigator site. Self-collection is not allowed at scheduled visits when the subject should be in stable condition.

Note: The sputum samples collected during AECOPD should preferably be obtained before administration of the first dose of antibiotics to treat the AECOPD (if applicable).

Refer to the SPM and to the central laboratory manual for more details and guidance on collection and handling of sputum samples.

6.9.16. Check contraindications to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Section 7.5 for more details on contraindication and on study procedures for subjects meeting contraindications to subsequent vaccination before administration of vaccine Dose 2.

6.9.17. Assess pre-vaccination body temperature

The oral or axillary body temperature of all subjects needs to be measured prior to any study vaccine administration. If the subject has fever (fever is defined as temperature ≥ 37.5°C/99.5°F) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 8).

6.9.18. Study group and treatment number allocation with randomisation

Study group and treatment number allocation will be performed as described in Section 6.2.2.2. The number of each administered treatment must be recorded in the eCRF.

6.9.19. Vaccination

After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly in the deltoid of the non-dominant arm (refer to Section 7.3 for a detailed description of the vaccines' administration procedure).

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (see Table 8).

The subjects will be observed closely for at least 60 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

6.9.20. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 7.6.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 7.7.

6.9.21. Recording of AEs, SAEs, pregnancies and pIMDs

- Refer to Section 9.3 for procedures for the investigator to record AEs, SAEs, pregnancies and pIMDs. Refer to Section 9.4 for guidelines and how to report SAE, pregnancy and pIMD reports to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.
- At Screening visit, electronic Diary Cards will be distributed to the subject. The subject will be instructed to measure and record the oral or axillary body temperature, and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days). Any solicited AE ongoing after Day 7 will be ***followed*** in the eDiary until resolution (for a maximum of 30 days). **(Amended 27 March 2019)**
- Any unsolicited AEs (i.e. on the day of vaccination and during the next 29 days occurring after vaccination) will be collected during discussion with the subject at subsequent study visit(s) and Phone Call(s).
- The investigator will transcribe the collected unsolicited AEs into the eCRF in English.

6.9.22. Train subjects on the use of electronic Diary Card and assign electronic Diary Card to subject

During the Screening Visit, subjects will be trained on how to use their electronic Diary Card.

At Visit 1, the investigator should evaluate whether or not the subject will be able to comply with the daily completion of the electronic Diary Card throughout the study (based on electronic Diary Card completion between Screening and Visit 1).

Compliance with electronic Diary Card completion implies that subject learns how to translate his/ her respiratory symptoms in answers to the questions as well as acquiring the technical expertise to use the device. Refer to the SPM for recommendations on what is considered adequate compliance by Visit 1.

Subjects for whom the investigator thinks they will not comply will be considered Screening failures.

During the learning period in-between Screening and Visit 1, the site staff will follow electronic Diary Card completion closely and should provide timely input/guidance to ensure that the subject reaches the targeted learning curve.

In addition, site staff will pro-actively monitor electronic Diary Card compliance throughout the study and provide the necessary input to maintain compliance.

6.9.23. Distribution of Subject Card

For information regarding the Subject Card, please refer to Section 9.9.

6.9.24. Healthcare Resource Utilisation

Healthcare use for each COPD patient will be obtained through review of the subject's medical record (aided by subject self-reporting). Healthcare Resource Utilisation includes all unscheduled visits to a physician office, visits to urgent care, visits to emergency department, and hospitalizations. Healthcare use should be recorded in eDiary and reported in the eCRF at study visit. Refer to the SPM for more details and guidance on recording of Healthcare Resource Utilisation.

6.9.25. HRQOL questionnaires

The subject should self-complete the questionnaires on HRQOL (CAT and SGRQ-C), which will be provided electronically via the eDiary, during specified study visits as detailed in Table 6 and Table 7.

All data from the HRQOL questionnaires will be transferred directly from the eDiary to GSK Biologicals.

Refer to the SPM for more details and guidance on the HRQOL questionnaires.

6.9.26. Confirm AECOPD and record its start date

Indicate the start date of each confirmed AECOPD in the eCRF.

6.9.27. Document AECOPD severity and end date

Indicate the severity and end date of each confirmed AECOPD in the eCRF. Refer to Table 1 for severity grading of AECOPD and to Section 4.1.1 for determination of end date.

6.9.28. Screening conclusion

The investigator will:

- Review data collected to ensure accuracy and completeness.
- Complete the Screening conclusion screen in the eCRF.

For Screening failures, only informed consent, demographic data, inclusion/ exclusion criteria, SAEs related to study participation that occurred after signing the informed consent and the Screening conclusion pages need to be completed in the eCRF. For other activities, 'not done' can be indicated.

For subjects who are Screening failures only for reasons that are expected to be temporary (e.g. fever), a re-Screening may be organised during which a limited number of Screening procedures need to be repeated (see also Table 6).

6.9.29. Study conclusion

The investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

6.10. Biological sample handling and analysis

Please refer to the SPM and Central Laboratory investigator manual for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

6.10.1. Use of specified study materials

When materials are provided by GSK Biologicals and/or a central laboratory, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 11.5 for the definition of cohorts to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals and/or a central laboratory does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM and to the Central Laboratory investigator manual.

6.10.2. Biological samples

Table 9 Biological samples

Sample type	Quantity	Unit	Timepoints	Sub-Cohort
Blood for humoral immunogenicity	~20	ml	• Visit 1 (Day 1) • Visit 2 (Day 31) • Visit 3 (Day 61) • Visit 4 (Day 91) • Visit 6 (Day 271) • Visit 8 (Day 451)	All enrolled subjects
Blood for humoral immunogenicity	~5	ml	• During each AECOPD	All enrolled subjects
Blood for CMI	~40	ml	• Visit 1 (Day 1) • Visit 4 (Day 91) • Visit 6 (Day 271) • Visit 8 (Day 451)	Sub-cohort for CMI *
Blood for biomarker, serum and plasma	~13	ml	• Visit 1 (Day 1) • Visit 8 (Day 451) • During each AECOPD	All enrolled subjects
Blood for biomarkers; haematology parameters	~2.0	ml	• Visit 1	All enrolled subjects
Sputum	1	Sample	• Visit 1 (Day 1) • Visit 4 (Day 91) • Visit 5 (Day 181) • Visit 6 (Day 271) • Visit 7 (Day 361) • Visit 8 (Day 451) • During each AECOPD	All enrolled subjects

* Refer to Section 5.1 for sub-cohort description.

6.10.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

Humoral antibody responses

Total IgG concentrations will be measured by ELISA at GSK Biologicals' laboratory or a GSK designated laboratory using qualified procedures.

Table 10 Humoral Immunity (Antibody determination) (Amended 27 March 2019)

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.

** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Other assays may be developed and/or validated on blood samples with the aim to measure the immune response to any component of either the NTHi-Mcat investigational vaccines and/or to other respiratory pathogens. The research may include, but is not limited to, functional assays such as serum bactericidal activity assays against NTHi and/or Mcat.

Cell-mediated immune responses

CMI assays will be performed at GSK Biologicals or GSK designated laboratory using qualified procedures.

Table 11 Cell-Mediated Immunity (CMI)

System	Component	Scale	Method	Unit	Laboratory
PBMCs	Specific $CD4^+$ T-cells	Quantitative	Flow cytometry ICS	Number of specific $CD4^+$ T-cells /10^6	GSK Biologicals* or GSK designated laboratory

PBMC = peripheral blood mononuclear cell; **ICS** = intracellular cytokine staining

* GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Additional vaccine antigen-specific $CD8^+$ T-cells data will be generated on peripheral blood mononuclear cells (PBMCs) in context of the specific $CD4^+$ T cell data generation by ICS.

Additional testing on peripheral blood mononuclear cells (PBMCs), such as, but not limited to, evaluation of NTHi and/or Mcat-specific memory B-cells, intracellular cytokine staining (ICS) testing using other bacterial antigens, may be done during the study or after study completion, should these data be required for accurate interpretation of the data and/ or for further research related to the investigational vaccine and/ or the

disease, should such test(s) become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Plasma of the CMI sub-cohort will be obtained during the processing of whole blood to obtain PBMCs and will be stored for potential future analyses and/ or assay development purposes.

Microbiological assessments

The quality of sputum samples will be assessed at the investigator's institution and/ or at a laboratory designated by GSK Biologicals by Gram staining.

Identification and semi-quantitative assessment of **potential bacterial pathogens** will be performed on fresh sputum samples using **conventional bacteriological** methods at the investigator's institution and/ or at a laboratory designated by GSK Biologicals on a subset of subjects ***(50% of subjects)*** according to local laboratory procedures and agreed identification methods (potential pathogens including, but not necessarily limited to identification of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus* and *P. aeruginosa*).

Identification of potential bacterial pathogens (including, but not necessarily limited to, *H. influenzae, S. pneumoniae*, *M. catarrhalis, S. aureus*, *P. aeruginosa* and *Streptococcus pyogenes* [*S. pyogenes*]) and quantification (for *H. influenzae*, *S. pneumoniae, M. catarrhalis*) on frozen sputum samples will be performed at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals using qualified molecular methods such as multiplex real time PCR and/ or quantitative PCR (qPCR).

Further **bacterial characterisation** on frozen isolates of *H. influenzae* and/or *M. catarrhalis* will be done at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using either standard agglutination techniques or molecular tools, such as PCR, microarray serotyping and/or sequencing.

Viral pathogen identification (including, but not necessarily limited to, respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) on frozen sputum samples will be performed using multiplex PCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using standardised and optimised procedures.
In addition, viral pathogens (such as enterovirus/rhinovirus) in frozen sputum samples will be quantified on all samples or a subset of samples (i.e. enterovirus/rhinovirus-positive sputum samples) using qPCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using standardised and optimised procedures.

Table 12 Sputum assessments

Number of subjects	Group	Visit no.	Pathogen to identify	Type of sample	Method	Testing Laboratory
Quality assessment						
~600	Both	1 4 5 6 7 8 AECOPD visits	Please refer to SPM and/or Central Laboratory Manual for components tested	Fresh sputum	Gram staining	Investigator institution or GSK designated laboratory
Bacterial pathogen identification						
~300*	Both	1 4 5 6 7 8 AECOPD visits	*H. influenzae*	Fresh sputum	Standard bacteriological identification methods and ***semi-***quantitative ***assessment.***	Investigator institution or GSK designated laboratory
				Isolate	***H. influenzae species confirmation and when possible Hi/NTHi differentiation*** by PCR	GSK Biologicals' ** or designated laboratory
			M. catarrhalis	Fresh sputum	Standard bacteriological identification methods and ***semi-***quantitative ***assessment***.	Investigator institution or GSK designated laboratory
			S. pneumoniae, P. aeruginosa, S. aureus, other potential pathogen	Fresh sputum	Standard bacteriological identification methods and ***semi-***quantitative ***assessment***.	Investigator institution or GSK designated laboratory

Number of subjects	Group	Visit no.	Pathogen to identify	Type of sample	Method	Testing Laboratory
~600	Both	1 4 5 6 7 8 AECOPD visits	*H. influenzae****, *M. catarrhalis,* *S. pneumoniae*	Frozen sputum	Multiplex bacterial pathogen quantitative PCR assay	GSK Biologicals' ** or designated laboratory
			S. aureus, Group A streptococci, *P. aeruginosa*		Multiplex bacterial pathogen qualitative PCR assay	
Viral pathogen identification						
~600	Both	1 4 5 6 7 8 AECOPD visits	Respiratory viral pathogens (including respiratory syncytial virus, parainfluenza virus, enterovirus**,** rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus)	Frozen sputum	Multiplex viral pathogen qualitative PCR assay	GSK Biologicals** or designated laboratory
~600 or Subset (enterovirus***/rhinovirus*** positive samples)	Both		Rhinovirus	***Frozen sputum***	quantitative PCR assay	GSK Biologicals** or designated laboratory

Number of subjects	Group	Visit no.	Pathogen to identify	Type of sample	Method	Testing Laboratory
Biomarker identification and quantification						
Patients not in culture subset*	Both	1 4 5 6 7 8 AECOPD visits	Inflammatory cytokines (such as TNF-α, IL-1, IL-8, IL-6)	Frozen sputum	Quantitative ELISA, multiplex CBA, ECL or PCR assays	GSK Biologicals** or designated laboratory

AECOPD = Acute exacerbation of chronic obstructive pulmonary syndrome; **SPM** = Study Procedures Manual; ***H. influenzae*** and **Hi** = *Haemophilus influenzae*; ***M. catarrhalis*** = *Moraxella catarrhalis*; **PCR** = Polymerase Chain Reaction; ***S. pneumoniae*** = *Streptococcus pneumoniae*; ***S. aureus*** = *Staphylococcus aureus*; **TNF** = Tumor Necrosis Factor; **IL** = Interleukin; **ELISA** = Enzyme Linked Immunosorbant Assay; **CBA** = Cytometric bead assay; **ECL** = Electrochemiluminescence.

*Testing will only be performed on a subset of 50% of the subjects.

**GSK Biologicals laboratory refers to the pre-clinical team or the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

***The PCR assay can detect and quantify H. influenzae in sputum samples. It can be assumed 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.

Sputum samples might also be used for **assay development**, such as assays for diagnostic purposes or for microbiome analysis.

Additional testing on frozen sputum samples (such as, but not limited to, qPCR for other bacterial and/or viral pathogens, quantitative serotype-specific PCR, microarray typing, sequencing, 16S RNA for microbiome analysis, presence (and/or concentration) of inflammatory cytokines) may be done during the study or after study completion, should these data be required for accurate interpretation of the study data and/ or for further research related to the investigational vaccine and/ or to respiratory diseases, should such test(s) become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Biomarkers

Table 13 Biomarkers

System	Component	Method	Scale	Laboratory
Plasma	Fibrinogen	Per contract laboratory's procedures	Quantitative	GSK Biologicals** or GSK designated lab
Serum	hsC-reactive protein (hsCRP)			
Serum	CXCL10 (IP-10)			
Whole blood	Leukocytes (White Blood Cells) Neutrophils * Lymphocytes * Eosinophils * Basophils * Monocytes * Erythrocytes (Red Blood Cells) Hemoglobin Platelets			

CXCL10 (IP-10) = C-X-C motif chemokine 10 (interferon gamma-induced protein 10)
*For white blood cell differential counts
**GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

The presence of other selected biomarkers might be evaluated.

Additional exploratory testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These assays may not be represented in the objectives/endpoints of the study protocol.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

6.10.4. Biological samples evaluation

6.10.4.1. Immunological read-outs

Table 14 Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Vacc 1	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
				Fibrinogen, hsCRP, IP-10 and haematology profile*
		Sub-cohort for CMI	~120	Specific $CD4^+$ T-cell
Visit 2 (Day 31)	Post-Vacc 1	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
Visit 3 (Day 61)	Pre-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
Visit 4 (Day 91)	Post-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		Sub-cohort for CMI	~120	Specific $CD4^+$ T-cell
Visit 6 (Day 271)	Post-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		Sub-cohort for CMI	~120	Specific $CD4^+$ T-cell
Visit 8 (Day 451)	Post-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
				Fibrinogen, hsCRP and IP-10
		Sub-cohort for CMI	~120	Specific $CD4^+$ T-cell
During each AECOPD visit from first vaccination to study conclusion		All enrolled subjects	-	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
				Fibrinogen, hsCRP and IP-10

hsCRP = high-sensitivity C-reactive protein, **CMI** = cell-mediated immunogenicity, **IP-10** = interferon gamma-induced protein 10.

*Including: WBC, neutrophils, eosinophils, lymphocytes, basophils, monocytes, RBC, haemoglobin and platelets.

6.10.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the antigen(s) used in the candidate vaccine or licensed vaccine.

7. STUDY VACCINES AND ADMINISTRATION

7.1. Description of study vaccines

The candidate vaccine to be used has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The study vaccines are labelled and packed according to applicable regulatory requirements.

Table 15 Study vaccines

Treatment name	Vaccine/ product name	Formulation	Presentation	Volume to be administered	Number of doses
10-10-3/AS01E	NTHi-Mcat 10-10-3	PD=10µg; PE-PilA=10µg; UspA2=3.3µg	Freeze-dried antigens in monodose vial	0.5 ml	2
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid in monodose vial		
Placebo	Formulation buffer S9b	Na_2HPO_4=0.4mg; KH_2PO_4=56µg; NaCl=1,16mg; KCl=30µg; $MgCl_2$=15µg	Liquid in monodose vial	0.5 ml	2

MPL = 3-O-desacyl-4'-monophosphoryl lipid A; **QS-21** = Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation).

7.2. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccines.

7.3. Dosage and administration of study vaccines

Table 16 Dosage and administration

Type of contact and timepoint	Study group	Treatment name	Volume to be administered	Route [1]	Site		
					Location	Directionality[2]	Laterality[3]
Visit 1 (Day 1)	10-10-3-AS	10-10-3/AS01E	0.5 ml	IM	Deltoid	Upper	Non-dominant
	CONTROL	Placebo					
Visit 3 (Day 61)	10-10-3-AS	10-10-3/AS01E	0.5 ml	IM	Deltoid	Upper	Non-dominant
	CONTROL	Placebo					

[1]Intramuscular (IM)

[2]Directionality is a qualifier for further detailing the location of the vaccine administration (e.g. Upper, Lower)

[3]The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

The investigational NTHi-Mcat vaccine needs to be reconstituted. Please refer to the SPM for more detailed instructions on study vaccines preparation.

7.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 30% additional vaccine doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement vial number. The replacement numbers will be allocated by dose. The system will ensure, in a blinded manner, that the replacement vial matches the formulation the subject was assigned to by randomisation.

7.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the investigational NTHi-Mcat vaccine. If any of these events occur during the study, the subject must not receive additional doses but may continue other study procedures (see Section 6.5).

- Anaphylaxis following the administration of vaccine.
- Pregnancy.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Current immune-mediated disease other than COPD.
- Malignancy (excluding non-melanotic skin cancer and carcinoma in situ of the cervix, if considered cured) or lymphoproliferative disorder.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 9.1.5.1 for the definition of pIMDs.

The following events constitute contraindications to administration of the investigational NTHi-Mcat vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 6.5), or withdrawn at the discretion of the investigator (see Section 9.5).

- Moderate or severe AECOPD that is on-going or that has not been resolved for at least 7 days at the time of vaccination.
- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines at discretion of the investigator.

7.6. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator or delegate should question the subject about any medications/products taken and vaccinations received by the subject (including standard medication taken before vaccination collected at Screening and/or at Visit 1). This includes the subject's COPD medication.

7.6.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant vaccines/medications/products, except vitamins and dietary supplements, administered during the entire study period following the first dose of study vaccine (Day 1 to Day 451).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.5°C/99.5°F]. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.
- Any concomitant medications/products/vaccines listed in Section 7.6.2.
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered during the study period for the treatment of a SAE /pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.
- Any receipt of influenza vaccine up to 1 year before the first dose of study vaccine.
- Any receipt of pneumococcal vaccine at any time before the first dose of study vaccine. Approximate timing of receipt should be recorded.

7.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses for immunogenicity

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis for immunogenicity. See Section 11.5 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- A vaccine not foreseen by the study protocol administered during the period starting 30 days before and ending 30 days after each dose of vaccine*, with the exception of any influenza, pneumococcal vaccines or other routinely recommended vaccine which may be administered ≥ 15 days preceding or following any dose of study vaccine.

  * In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

- Immunoglobulins or any blood products administered at any time during the study period.

- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) at any time during the study period (e.g. methotrexate). Use of corticosteroids is allowed as per local treatment recommendations.

7.6.3. Concomitant medications/ products/ intervention that may lead to the elimination of a subject from the per-protocol analysis for efficacy

In addition to the concomitant medications/ products/ vaccines described in the Section 7.6.2, the use of the following medications/ products/ intervention will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis for efficacy.

- Underwent lung transplantation/ lung resection surgery at any time during the entire study period.
- Chronic use of antibiotics at any time during the entire study period.

7.7. Intercurrent medical conditions that may lead to elimination of a subject from per-protocol analyses

At each study visit subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the per-protocol cohort for immunogenicity and efficacy if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status.

8. HEALTH ECONOMICS

Not applicable.

9. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

9.1. Safety definitions

9.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Significant or unexpected worsening of the condition under study.
- Exacerbation of a chronic or intermittent pre-existing condition, apart from the condition under study, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 9.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/ SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease being studied, or expected progression, signs, or symptoms of the disease being studied, unless more severe than expected for the subject's condition.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

9.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

9.1.3. Solicited adverse events

Solicited local and general AEs occurring during a 7-day follow-up period after each vaccination (i.e. the day of vaccination and the 6 subsequent days), will be reported via eDiar*y* for vaccine reactogenicity. **(Amended 27 March 2019)** Unsolicited AEs occurring during a 30-day follow-up period after each vaccination (i.e. the day of vaccination and the 29 subsequent days), will be reported at Phone Contacts and Clinical Visits, and recorded via the appropriate section of the eCRF.

9.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 17 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

9.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 18 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Chills

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

Note: Subjects will be instructed to measure and record the oral or axillary body temperature in the evening. Should additional temperature measurements be performed at other times of day, subjects will be instructed to record the highest temperature in the eDiary.

9.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 9.1.1 and 9.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.1.5. Adverse events of specific interest

9.1.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 19.

However, 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.

Table 19 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy, - Multifocal motor neuropathy - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: - Diffuse Scleroderma - CREST syndrome • Idiopathic inflammatory myopathies, including: - Dermatomyositis - Polymyositis • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: - Juvenile Idiopathic Arthritis - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing Spondylitis, - Reactive Arthritis (Reiter's Syndrome), - Undifferentiated Spondyloarthritis, - Psoriatic Arthritis, - Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localised Scleroderma (Morphoea).

Vasculitis	Blood disorders	Others
• Large vessels vasculitis including: - Giant Cell Arteritis (Temporal Arteritis), - Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: - Polyarteritis nodosa, - Kawasaki's disease, - Microscopic Polyangiitis, - Wegener's Granulomatosis (granulomatosis with polyangiitis), - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), - Buerger's disease (thromboangiitis obliterans), - Necrotizing vasculitis (cutaneous or systemic), - anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), - Henoch-Schonlein purpura (IgA vasculitis), - Behcet's syndrome, - Leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: - IgA nephropathy, - Glomerulonephritis rapidly progressive, - Membranous glomerulonephritis, - Membranoproliferative glomerulonephritis, - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: - Autoimmune uveitis - Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory Bowel disease, including: - Crohn's disease, - Ulcerative colitis, - Microscopic colitis, - Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type I. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) corresponding to the above diagnoses will be available to investigators at study start as presented in APPENDIX C. The list of PTs was created using MedDRA version 20.1.

9.2. Events or outcomes not qualifying as adverse events or serious adverse events

9.2.1. AECOPD

AECOPD are common in subjects with COPD. Because they are typically associated with the disease under study, only AECOPD meeting the definition of an SAE and occurring in the time period defined in Section 9.3.1 will be reported to GSK Biologicals as described in Sections 9.4.1 and 9.4.3.

9.2.2. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccines but may continue other study procedures.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 9.4.1 and 9.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccines will be reported to GSK Biologicals as described in Section 9.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

9.3. Detecting and recording adverse events, serious adverse events and pregnancies

9.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs starting within 29 days following administration of each dose of study vaccines (Day 1 to Day 30) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccines and will end at last study visit for each subject. See Section 9.4 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccines.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccines and will end at last study visit. See section 9.4 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccines and will end at last study visit. See section 9.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 20.

Table 20 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 months post Dose 2	Study Conclusion
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.

9.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 20. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study vaccines, the investigator will promptly notify the Study Contact for Reporting SAEs.

9.3.3. Evaluation of adverse events and serious adverse events

9.3.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccines or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

9.3.3.2. Assessment of adverse events

9.3.3.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 21 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Chills	0	None
	1	Chills that are easily tolerated
	2	Chills that interfere with normal activity
	3	Chills that prevent normal activity

*Fever is defined as temperature ≥ 37.5°C/99.5°F. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals using the following grading scale:

0 : < 20 mm diameter

1 : ≥ 20 mm to ≤ 50 mm diameter

2 : > 50 mm to ≤ 100 mm diameter

3 : > 100 mm diameter

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

0 : < 37.5°C

1 : 37.5°C to 37.9°C

2 : 38.0°C to 38.9°C

3 : ≥ 39.0°C

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

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

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.1.2.

9.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccines and the occurrence of each unsolicited AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the AE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccines will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

All solicited local (injection site) and general reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the study vaccine?

YES	:	There is a reasonable possibility that the study vaccines contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccines. There are other, more likely causes and administration of the study vaccines is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as ‘serious’ (see Section 9.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

9.3.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

9.4. Reporting of serious adverse events, pregnancies, and other events

9.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 22, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 22, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 22, once the investigator determines that the event meets the protocol definition of a pIMD.

AECOPD (Section 4) that meet the criteria of a SAE (Section 9.1.3) that occur in the time period defined in Section 9.3 should also be recorded in eCRF as "AECOPD visit" or as "Missed AECOPD visit". **(Amended 27 March 2019)**

Table 22 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD
‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.

9.4.2. Contact information for reporting serious adverse events, pregnancies and pIMDs

Study Contact for Reporting SAEs, pIMDs and pregnancies
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, pIMDs and pregnancies
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD or PPD Email address: PPD US sites only: Fax: PPD Canadian sites only: Fax: PPD

9.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

9.4.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

9.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

9.4.5. Reporting of pIMDs to GSK Biologicals

Once a ***new onset of a pIMD or exacerbation of a pre-existing*** pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. **(Amended 27 March 2019)** The report allows to specify that the event is a pIMD and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the pIMD.

Refer to Section 9.4.3.1 for back-up system in case the electronic reporting system does not work.

9.4.6. Updating of SAE, pregnancy, and pIMD information after removal of write access to the subject's eCRF

When additional SAE, pregnancy, or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 22.

9.4.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 9.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the study vaccines and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

9.5. Follow-up of adverse events, serious adverse events, and pregnancies

9.5.1. Follow-up of adverse events and serious adverse events

9.5.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 22).

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

All pIMDs (serious or non-serious) and SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

9.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, pIMDs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

9.5.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

9.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of SAEs / pIMDs should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.6).

9.7. Unblinding

GSK Biologicals' policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the study vaccines, prior to regulatory reporting. The GSK Biologicals' Central Safety Physician is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 9.4.1).

9.8. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice or needs the support of GSK to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

GSK Biologicals' Contact information for Emergency Unblinding **24/24 hour and 7/7 day availability**
GSK Biologicals' Central Safety Physician: Outside US/Canada: PPD (GSK Biologicals Central Safety Physician on-call) For US/Canada only: PPD (GSK Biologicals Central Safety Physician on-call) **GSK Biologicals' Central Safety Physician Back-up:** Outside US/Canada: PPD US/Canada only: PPD **Emergency Unblinding Documentation Form transmission:** Outside US & Canada: Fax: PPD or PPD US/Canada only: Fax: PPD

9.9. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject. In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times during the study duration.

9.10. Safety monitoring

9.10.1. Safety Review Team

The project's SRT includes as core members the GSK Biologicals' Central Safety Physician, the Clinical Research & Development Lead (CRDL), Epidemiologist, Clinical Regulatory Affairs representative and the Biostatistician of the project. The SRT is responsible for on-going safety monitoring of the entire project and SRT meets if there is a need to perform a data review, or if there is a safety problem (at least once per year). The SRT will inform the iSRC about any potential safety concern relevant to the study.

Before each iSRC safety evaluation in this study, the SRT will review the same safety data, but in a *blinded* manner, in order to keep all people involved in the conduct, cleaning and final analysis of the study blinded.

9.10.2. Internal Safety Review Committee

The iSRC will be authorised by GSK Biologicals' Vaccine Safety Monitoring Board (VSMB) and its core members will include a GSK Biologicals' Safety Physician, a CRDL, and a Biostatistician who are not otherwise involved in the conduct of the project. If none of the core members listed above is a respiratory expert, such an expert will be included.

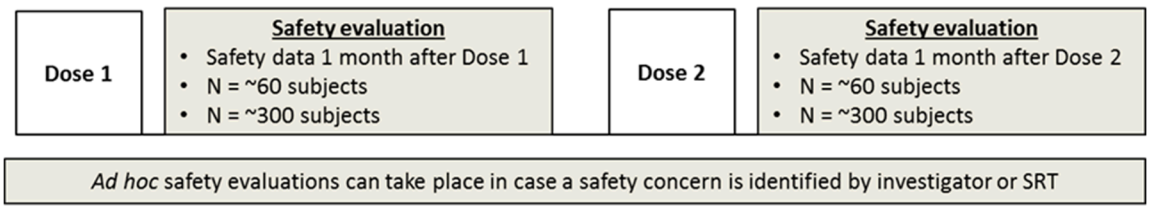
The iSRC will conduct *unblinded* reviews of all available safety data from the present study while taking into account any other findings that could have an impact on the safety of the subjects, and will determine whether there is a safety signal that needs to be escalated to GSK Biologicals' VSMB.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

Planned iSRC reviews will be done when approximately 60 and 300 subjects have completed one month after first vaccination and when approximately 60 and 300 subjects have completed one month after second vaccination (Figure 3).

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

Details about the working of the iSRC will be documented in an iSRC Charter.

Figure 3 Overview of iSRC evaluation



10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

10.2. Subject withdrawal

Withdrawals will not be replaced.

10.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt (e.g. 3 telephone calls and a certified letter to the last known address) to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 9.5.1.2).

10.2.2. Subject withdrawal from study vaccines

A 'withdrawal' from the study vaccines refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccines may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity ***according to protocol procedure.*** **(Amended 27 March 2019)**

Information relative to premature discontinuation of the study vaccines will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

10.3. Extension study

During the study conclusion visit, the investigator will ask each subject if they are interested to participate in an extension study, if planned. If a subject is not interested in participating in an extension study the reason for refusal will be documented in the subject's eCRF.

10.4. Screening failures

Screening failures are defined as subjects who are withdrawn from the study after giving informed consent, but who do not meet the inclusion and exclusion criteria.

The following information will be collected for screening failures:

- Informed consent.
- Demographic data.
- Inclusion/exclusion criteria.
- SAEs related to study participation that occurred after signing informed consent.
- Screening conclusion.

11. STATISTICAL METHODS

11.1. 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.

11.2. 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.

11.3. Tertiary endpoints

Sputum sample PCR:

- Occurrence (presence and absence)***, acquisition, apparition,*** 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. **(Amended 27 March 2019)**

Sputum sample culture:

- Occurrence (presence and absence)***, acquisition, apparition,*** 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. **(Amended 27 March 2019)**
- 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 score 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.

11.4. Determination of sample size

Primary objective - Efficacy: All (causes) of moderate and severe AECOPD

The primary objective of this study is to assess the efficacy of the investigational vaccine as compared to placebo control, as measured by the rate of moderate and severe AECOPD from 1 month after second dose of vaccination till 1 year after. Sample size is computed based on the probability to detect a clinically relevant effect. Sample size is estimated using a formula from [Keen, 2007]. Assuming a yearly incidence rate of moderate and severe AECOPD in the placebo arm equal to 0.8 per subject [Mackay, 2012; Dransfield, 2013] and an over-dispersion parameter of 1.8, ~300 subjects per group will provide 80% power to detect at least a 28% reduction in the rate of AECOPDs in the vaccinated group compared to the placebo group, with a 1-sided 6.5% significance level and a dropout rate of 15%.

Table 23 presents sample size under different assumption for over-dispersion parameter and AECOPD incidence rate in placebo arm, assuming a VE=28%, a drop-out of 15% (85% of enrolled subjects are expected to complete one year follow up) and 1:1 randomization ratio.

Table 23 Total number of subjects for primary endpoint

Overdispersion factor*: 1.8				
2-side α-level	**Rate in Placebo**	**Rate in Treatment**	**N per group**	**Total Sample size****
13%	0.9	0.648	228	536
10%	0.9	0.648	254	596
13%	0.8	0.576	257	604
10%	0.8	0.576	286	672
13%	0.7	0.504	293	690
10%	0.7	0.504	327	768
13%	0.6	0.432	342	804
10%	0.6	0.432	381	896
Overdispersion factor*: 2				
13%	0.9	0.648	251	590
10%	0.9	0.648	280	658
13%	0.8	0.576	282	664
10%	0.8	0.576	314	740
13%	0.7	0.504	323	760
10%	0.7	0.504	360	846
13%	0.6	0.432	376	886
10%	0.6	0.432	419	986

Sample size calculated from a formula from Keen, 2007 implemented on SAS.
* Overdispersion factor for a Poisson distribution.
**Total sample size takes in to account 15% drop-out rate.

Secondary objective - Efficacy: mild and moderate AECOPD associated to bacteriological pathogens (PCR).

One of the secondary objectives is to assess efficacy of the investigational vaccine compared to placebo, as measured by the rate of moderate and severe AECOPD associated to NTHi and/or Mcat (detected by PCR), starting from 1 month after second dose of vaccination till 1 year after.

Assuming an incidence rate of AECOPD (all causes) equal to 0.8 per subject per year, a vaccine efficacy of 70% against AECOPD associated with NTHi and/or Mcat and assuming that 25% of AECOPDs are associated with NTHi and 15% with Mcat [Wang, 2015; Garcha, 2012], Table 24 shows the sample size requested for the bacteriological endpoint, assuming a rate of loss sputum samples equal to 20%.

Table 24 Sample size for secondary bacteriological endpoint

All AECOPD Rate	NTHi	Mcat	2-side α-level	Beta	N per group	Sample** size
0.8	20%	10%	13%	0.2	308	908
0.8	25%	15%	13%	0.2	218	642
0.8	20%	10%	10%	0.2	339	998
0.8	25%	15%	10%	0.2	237	694
0.8	20%	10%	13%	0.3	248	730
0.8	25%	15%	13%	0.3	175	514
0.8	20%	10%	10%	0.3	276	810
0.8	25%	15%	10%	0.3	196	578

Sample size calculated from a formula from Keen, 2007 implemented on SAS.
**Total sample size takes in to account for 15% of subject drop-out and 20% of samples lost.

Study is planned to enrol approximately 600 subjects (~300 in each arm), assuming a subject drop-out rate of 15% and a loss of sputum samples of 20%, we have a power of 77.5% to detect a reduction in AECOPDs associated with NTHi and/or Mcat of at least 70% of vaccine efficacy with a 1-sided 6.5% significance level.

11.5. Cohorts for analyses

The following study cohorts will be evaluated.

11.5.1. All enrolled set

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

11.5.2. Total vaccinated cohort

The total vaccinated cohort (TVC) will include all subjects with at least 1 documented study vaccine administration, with respect to the vaccine actually administered:

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

In subjects receiving only one dose the efficacy endpoint is the number of moderate or severe AECOPD (any cause), occurring within a period starting from Day 90 and lasting for 1 year (until study conclusion).

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

11.5.3. 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.

11.5.4. Per-protocol *set* for analysis of immunogenicity

The per-protocol set (PPS) for immunogenicity 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, as specified in Table 8.
- 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 (see Section 7.6.2) up to the 1 month post--Dose 2 visit (Day 91).
- Who did not present an intercurrent medical condition leading to elimination from the PPS analysis for immunogenicity (see Section 7.7), up to the 1 month post--Dose 2 visit (Day 91).
- Who complied with the blood sample timings as specified in Table 8, at the 1 month post-Dose 2 visit (Day 91).
- For whom post-vaccination immunogenicity results are available for at least 1 assay.

11.5.5. Per-protocol *set* for analysis of efficacy

The 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, as specified in Table 8.
- Who received the study vaccine according to protocol procedures.
- Not having received a medication/ product/ vaccine that may lead to elimination from the PPS (per-protocol) analysis for efficacy (see Section 7.6.3).

In addition, for the Bacteriological efficacy endpoints:

- For whom the sputum sample results are available.

11.5.6. *Full Analysis set (FAS)*

The FAS will include all randomized subjects who will receive at least 1 vaccine administration. As per intention-to-treat 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).

11.6. Derived and transformed data

The study groups will be defined by treatment actually administered at Dose 1.

Demography

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

Efficacy – Clinical Endpoint

- For a given subject and a given efficacy measurement, missing or unevaluable measurements will not be imputed. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missing is assumed to be Missing Completely at Random (MCAR) or Missing At Random (MAR) only.
- 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. The number of exacerbations during the 1-year follow-up period 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 purposes of reporting summary statistics since the modelling of exacerbations takes into account the number of exacerbations and the time of follow-up for each subject.
- 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.
- The calculation of exacerbation rate will be based on follow-up period intervals to avoid obtaining high imputed rates if a subject withdrew very early in the follow-up period after experiencing an exacerbation. Since treatment courses for moderate/severe exacerbations are ≤ 2 - 4 weeks when appropriate, calculated numbers of exacerbations for subjects withdrawing from the study will be based on 4-week intervals of the follow-up period. For subjects followed for less than 1 year, the number of exacerbations during the 1-year follow-up period will be calculated by multiplying the number of exacerbations experienced by the subject by 13 and dividing by the number of 4-week periods the subject was followed up [Stockley, 2006]:

  Number of exacerbations per year = Number of exacerbations * 13 /Number of 4-week treatment period intervals.

Safety

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

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.

Immunogenicity

- Calculation of the GMCs will be performed by taking the anti-logarithm in base 10 (anti-log10) of the mean of the log10 concentration transformations.
- Antibody concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of geometric mean concentration (GMC) calculation.
- A seronegative subject is defined as a subject whose antibody concentration is below the assay cut-off value (i.e. the ELISA lower limit of quantification).
- A seropositive subject is defined as a subject whose antibody concentration is greater than or equal to the assay cut-off value (i.e. the ELISA lower limit of quantification).
- For a given subject and the analysis of a given immunogenicity measurement, missing or unevaluable measurements will not be replaced.

CMI

- The frequency of $CD4^+$ T-cells producing two or more markers (such as CD40 Ligand (CD40L), interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), upon in vitro stimulation with the antigen (induction condition) is presented per million of $CD4^+$ T cells for the analysis and in percent 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 among IFN-γ, IL-2, IL-13, IL-17, TNF-α and/or CD40L, upon in vitro stimulation with the antigen (induction condition) minus the frequency of $CD4^+$ 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.

- The frequency of $CD4^+$ T-cells expressing a marker (such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α) upon *in vitro* stimulation with the antigen (induction condition) is presented per million of cells for the analysis and per hundred cells for the graphical representation.
- Values less or equal to zero will be set to 1 for the purpose of the analysis.
- The Geometric Mean (GM) frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations.

HRQOL

- The CAT index will be derived as the sum of the ratings recorded for each of the eight individual items. Each of these items has 6 possible scores (0, 1, 2, 3, 4 or 5), leading to a range of 0 to 40 for CAT score.
- The SGRQ-C score will be grouped in total scores and by three component scores: Symptoms, Activity, Impacts. Score are assigned following the SGRQ-C Manual.

11.7. Analysis of demographics

Demographic characteristics (age at the first dose in years, gender, geographical ancestry, smoking status) and cohort description will be summarised by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as gender; geographical ancestry, age category, smoking status;
- Mean, median and standard deviation will be provided for continuous data such as age.

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

Withdrawal status will be summarised by group using descriptive statistics:

- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal;
- The number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses will be tabulated.

No inferential analyses of demographic data are planned.

11.8. Analysis of efficacy

The primary analysis will be performed on the mTVC and repeated on the TVC ***and the FAS***. The primary analysis will also be repeated on the efficacy ATP (per-protocol) cohort if the percentage of vaccinated subjects excluded from the ATP cohort for efficacy is more than 5%.

Efficacy – Clinical Endpoint

The following incidence rates of AECOPD (any type) occurring from enrolment up to 1 month post-Dose 2 will be computed together with ***95%*** CI, 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%*** CI**:**

- All-cause moderate and severe AECOPD (primary endpoint).
- All-cause, all-severity AECOPD.
- All-cause AECOPD, by severity.

For the primary endpoint, the 87% CI will also be reported in order to evaluate the null hypothesis at 13% alpha level (2-side). This objective will be considered a success if the lower limit of the 87% CI will be above 0%. **(Amended 27 March 2019)**

The CIs of the incidence rate will be computed using a model which accounts for repeated events. 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 years or 60–80 years), GOLD grade (2, 3 or 4), history of 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. If the model does not converge, the Poisson distribution will be used instead of the Negative Binomial one.

VE for AECOPD events is defined as:

$$VE\ (AECOPD) = 1 - R_{vacc} / R_{con}$$

with:

- 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 Control group.

Incidence rates of AECOPD (any type) and VE, together with 95% CI, will be computed for the following time periods:

- At Month 3, 6, 9, 12, 15 from Day 1 (cumulative)
- By 6 Months follow up period (from 1 month post-Dose 2)
- By 3 Months follow up period (from 1 month post-Dose 2)

The model usd will be the same as for the primary analysis.

A sensitivity analysis ***using*** a permutation test will be performed for the primary efficacy endpoint.

Efficacy – Bacteriological Endpoint (PCR)

Similarly, VE in prevention of NTHi and/or Mcat associated AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year and its 95% CI will be computed, with the following incidence rate:

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

The proportion of sputum samples with exact 95% CI obtained at each visit (scheduled visits and AECOPD-driven visits) and positive for bacterial pathogens (overall and by bacterial pathogen) will be computed by group and overall. The exact CIs will be estimated assuming independence of bacterial results across sputum samples.

Incidence rates of AECOPD associated to NTHi and/or Mcat, and VE, together with 95% CI will be evaluated for the following time periods:

- At Month 3, 6, 9, 12, 15 from day 1 (cumulative)
- At 6 months follow up period (from 1 month post-Dose 2)
- At 3 months follow up period (from 1 month post-Dose 2)

The model used will be the same as for the primary analysis. All above analyses will be performed in sputum samples using PCR. **(Amended 27 March 2019)**

Efficacy – Bacteriological Endpoint (culture)

Same set of analyses, as in the bacteriological efficacy endpoints, will be performed in the subset of culture sputum data.

Incidence rates of AECOPD associated to NTHi and/or Mcat, and VE, together with 95% CI will be evaluated for the following time periods:

- At Month 3, 6, 9, 12, 15 from day 1 (cumulative)
- At 6 months follow up period (from 1 month post-Dose 2)
- At 3 months follow up period (from 1 month post-Dose 2)

The model used will be the same as for the primary analysis. All above analyses will be performed in sputum samples using PCR. **(Amended 27 March 2019)**

Bacteriological load

The following will be performed in PCR and culture samples:

- Percentage of subjects with *H. influenzae* and *M. catarrhalis* in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451, per group.
- Relative abundance of *H. influenzae* and *M. catarralis* in sputum as measured by culture before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 and at each AECOPD visit, per group.
- Descriptive summaries of the presence and quantity of NTHi and/or Mcat and/or other bacteria at each planned visit will be provided for both culture (semi-quantitative estimation) and PCR analysis (copies/mL).

Acquisition and apparition

The following definitions will be used:

- ***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 (NT)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 apparition for each subject from Day 1), by treatment groups.*** **(Amended 27 March 2019)**

11.9. Analysis of immunogenicity

The analysis will be performed on the immunogenicity ATP (per-protocol) cohort. If the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is more than 10%, a second analysis will be performed on the TVC.

11.9.1. Within groups assessment

Humoral immune response

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

- Seropositivity rate (i.e, percentage of seropositive subject) and the associated exact 95% CI
- GMCs and the associated 95% CI

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

A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value, as specified in Table 10.

11.9.2. Between groups assessment

Comparative analyses will be exploratory with the aim to characterise the difference between the 2 groups in humoral immune response.

The difference in terms of GMCs will be evaluated at 1 month post-Dose 2 by computing 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).

11.9.3. Cell-mediated immune response

Cell-mediated immune response as part of secondary endpoints

CMI induced by the NTHi-Mcat candidate vaccine will be evaluated, presenting the frequencies of antigen-specific $CD4^+$ T cells per 10^6 cells. The specific $CD4^+$ T cells being identified as the $CD4^+$ T cells expressing at least 2 different cytokines/activation markers among CD40L, IL-2, TNF-α, IFN- γ, IL-13 and IL-17 upon *in vitro* stimulation. ***D***escriptive statistics (Min, Q1, Median, Q3 & Max) will be reported for each group at Day 1, Day 91, Day 271 and Day 451. **(Amended 27 March 2019)**

Cell-mediated immune response as part of tertiary endpoints

CMI response as the frequencies of specific $CD4^+$ T cells per 10^6 cells expressing any combination of cytokines/activation markers will be determined. In addition, the T helper profile of the specific T cell response in T helper 1, T helper 2 and T helper 17 based on the specific expression of respectively IFN-γ, IL-13 and IL-17 will be characterized. ***D***escriptive statistics (Min, Q1, Median, Q3 & Max) will be reported for each group at Day 1, Day 91, Day 271 and Day 451. **(Amended 27 March 2019)**

11.9.4. Analysis of selected biomarkers

Descriptive statistics (median, mean, range, standard deviation, first and third quartiles) will be tabulated for each selected biomarker at study start (Day 1) and end of the study (Day 451) and for each AECOPD from first vaccination to study conclusion.

11.9.5. Correlate of protection

An exploratory analysis will be implemented in an attempt to correlate immune responses to vaccination. A specific analysis plan will describe the methodologies to be used for that purpose.

11.10. Analysis of safety

The analysis will be performed on the TVC.

The percentage of subjects with at least one **local AE** (solicited and unsolicited), with at least one **general AE** (solicited and unsolicited) and with any AE during the 7-day (Day 1 – Day 7) or the 30-day (Day 1 – Day 30) follow-up period will be tabulated after each vaccination and overall with exact 95% confidence interval (CI). The same computations will be done for Grade 3 AEs, for related AEs and for Grade 3 related AEs.

The percentage of subjects/doses reporting each individual solicited local (any grade, Grade 3) and general (any grade, Grade 3, related, Grade 3 related) AE during the 7-day (Day 1 to Day 7) follow-up period will be tabulated for each group as follows:

- Overall, the percentage of subjects with the symptom and its exact 95% CI.
- Overall, the percentage of doses with the symptom and its exact 95% CI.

- Per study vaccine dose, the percentage of subjects with the symptom and its exact 95% CI.

The exact 95% CIs will be calculated assuming independence between doses. For fever, additional analyses will be performed by 0.5°C increments.

The verbatim reports of **unsolicited** symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate preferred term (PT). The percentage of subjects with unsolicited symptoms during the 30-day follow-up period after any study vaccine dose with its exact 95% CI will be tabulated by group and by MedDRA PT. Similar tabulation will be done for the percentage of doses, for Grade 3 unsolicited symptoms, for unsolicited symptoms that resulted in a medically attended visit, for Grade 3 and causally related unsolicited symptoms and for unsolicited symptoms causally related to vaccination.

The number of subjects who experienced any **pIMD** or any **SAE** from first vaccination up to 12 months post-Dose 2 will be reported.

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

Pregnancy from first vaccination up to study end for each female subject and pregnancy outcomes will be described in detail.

The percentage of subjects/ dose using **concomitant medication/ product** (any medication/ product, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (Day 1 – Day 7) and during the 30-day follow-up period (Day 1 – Day 30) will be summarised per group for each dose and overall per dose.

- **iSRC safety evaluations**

For safety, 4 interim analysis evaluations are planned. iSRC reviews will be done once 60 and 300 subjects complete one month after first vaccination and once 60 and 300 subjects complete one month after second vaccination (see Figure 3).

Unblinded review of safety data will be done during iSRC evaluations. No individual clinical study report will be written as a result of these safety evaluations.

11.10.1. Analysis of HRQOL, lung capacity

The analysis will be performed on the TVC.

Descriptive statistics (median, mean, range, standard deviation, first and third quartiles) on the **EXACT-PRO, CAT**, **SGRQ-C** scores, on **FEV_1% of predicted normal value** will be tabulated by specified visit.

11.11. Interpretation of analyses

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

Comparative analyses related to the secondary and tertiary objectives, with the aim to characterise the difference in reactogenicity/ immunogenicity/ efficacy between groups will be descriptive and should be interpreted with caution.

11.12. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

11.12.1. Sequence 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.

12. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, public disclosure requirements and publications must be fulfilled.

12.1. Case Report Form/electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

12.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

12.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the

investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

12.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

12.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

12.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

13. COUNTRY SPECIFIC REQUIREMENTS

13.1. Requirements for Germany

Explanatory statement concerning Gender Distribution (Article 7, paragraph 2 (12) of the German GCP ORDER)

For this NTHI MCAT-002 study, there is no intention to conduct specific analyses investigating the relationship between gender and the safety and efficacy of the investigational NTHi-Mcat vaccine. Recruitment will include males and females. To not expose pregnant women and their foetuses/children to an early-phase investigational vaccine, females enrolled in this trial will either be of non-childbearing potential (i.e., have a current tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or be premenarchal or postmenopausal), or if she is of childbearing potential, she must practice adequate contraception for 30 days prior to the beginning of the administration of study treatment, have a negative pregnancy test and continue such precautions during the entire study treatment period and for 2 months after completion of the injection series (Refer to the study protocol, Section 5.2 “Inclusion criteria” and Section 5.3 “Exclusion criteria”). The recruitment will be closed to females who are pregnant or lactating. Similarly, patients becoming or deciding to become pregnant during the study must stop the study treatment administrations.

Historically, COPD was considered a disease of males. The past few decades have seen a shift in this paradigm. In the United States, between the periods of the First National

Health and Nutrition Examination Survey (NHANES I) and NHANES III, the prevalence of spirometrically determined moderate COPD increased in women from 50.8 per 1000 to 58.2 per 1000, whereas the prevalence decreased in men from 108.1 per 1000 to 74.3 per 1000.3 Data from the National Health Interview Survey show that the self-reported prevalence of COPD in the United States was stable from 1998 through 2009 and has remained higher in women than in men. A similar trend is seen in other developed countries such as Canada, the Netherlands, and Australia [Aryal, 2013]. There are no reports of gender differences in the efficacy or safety outcomes for patients receiving the investigational NTHi-Mcat vaccine.

13.2. Requirements for France

This section includes all the requirements of the French law (n° 2004-806 of 9th August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol and includes specifics GSK requirements.

1. Concerning the «STUDY POPULATION»

- In line with the local regulatory requirements, the following text about «PAYMENT TO SUBJECTS» is added:

  Subjects will be paid for the inconvenience of participating in the study. The amount of payment is stated in the informed consent form. Subjects not completing the study for whatever reason could be paid at the discretion of the Investigator, generally on a pro rata basis.
- In line with the local regulatory requirements, the following text about «NATIONAL FILE» is added:

  All subjects who will be paid, will be recorded into the "National File" by the investigator. They could be identified and monitored under the «Fichier national».

  The following details will be described:

  – Reference of the study
  – Surname and first name
  – Date and place of birth
  – Sex
  – Dates of beginning and termination of the study
  – Exclusion period
  – The total amount of allowance.
- In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS» is added:

  A subject will be eligible for inclusion in this study if he/she is either affiliated to or beneficiary of a social security category.

It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

2. Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"

The expected number of patients to be recruited in France is declared to the French regulatory authority.

3. Concerning the "STUDY CONDUCT CONSIDERATIONS"

- In section "REGULATORY AND ETHICAL CONSIDERATIONS, INCLUDING THE INFORMED CONSENT PROCESS"
  - Concerning **the process for informing the patient** or his/her legally authorized representative, the following text is added:

    French Patient Informed Consent form is a document which summarizes the main features of the study and allows collection of the patient's written consent in triplicate. It also contains a reference to the authorisation of ANSM and the approval from the French Ethic committee and the maintenance of confidentiality of the returned consent form by GSK France.
  - Concerning **the management of the Patient Informed Consent forms**, the following text is added:

    The first copy of the Patient Informed Consent form is kept by the investigator. The second copy is kept by the Medical Direction of GSK France and the last copy is given to the patient or his/her legally authorized representative.

    The second copy of all the consent forms will be collected by the investigator under the Clinical Research Assistant's (CRAs) control, and placed in a sealed envelope bearing only:

    - the study number,
    - the identification of the Centre: name of the principal investigator and centre number,
    - the number of informed consents,
    - the date,
    - and the principal investigator's signature.

    Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.
- In section concerning the "NOTIFICATION TO THE HOSPITAL DIRECTOR" the following text is added:

  In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the

financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

- In section concerning the "INFORMATION TO THE HOSPITAL PHARMACIST" the following text is added:

  In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- In section "DATA MANAGEMENT" the following text is added:

  Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK Laboratory (Clinical Operations Department).

- In the section concerning "DEMOGRAPHIC DATA", the following text is added:

  In accordance with the data processing and freedom French law dated on 6th of January 1978 modified on the 6th of August 2004 - article 8, the ethnic origin can only be collected if the collection of this data is justified within the framework of this study.

- In the section concerning "TESTING OF BIOLOGICAL SAMPLES" the following text is added:

  In accordance with the Article L1211-2 of the French Public Health Code, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

4. Concerning the «SAE»

- In section "TRANSMISSION OF THE SAE REPORTS":

  In case of paper CRF, the SAE Reports have to be transmitted to the GSK France Drug Safety Department, which name, address and phone number are:

  Département de Pharmacovigilance

  Laboratoire GlaxoSmithKline

  23 rue François Jacob

  92500 RUEIL MALMAISON

  Tel : PPD

  Fax : PPD

  PPD

5. Monitoring visits

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GSK or of a service provider designated by GSK. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GSK or from a service provider designated by GSK. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GSK have direct access to all the data concerning the Study (test results, medical record, etc. …). This consultation of the information by GSK is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

6. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's eCRF use here below:

The Health Institution and the Investigator undertake:

- That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GSK or by a company designated by GSK.
- That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
- That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GSK.
- To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.

- That the Investigator and the staff of the investigator center enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.
- That the Investigator resolves and returns to GSK the data queries issued by GSK or a service provider designated by GSK within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GSK and/or a company designated by GSK.
- To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
- To return at the end of the Study the IT Equipment and/or access codes to GSK or to any company designated by GSK and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

7. CTR publication

It is expressly specified that GSK and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GSK GROUP named Clinical Trial Register (CTR) including the registration of all the clinical trials conduct by the GSK Group and this before or after the publication of such results by any other process.

8. Data Protection French Law of 6 January 1978 (CNIL)

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GSK to monitor and follow the implementation and the progress of the Study are declared with the CNIL by GSK. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GSK in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GSK Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

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APPENDIX A LABORATORY ASSAYS

Humoral immunity

Serological assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described below and in Table 10. The cut-off and unit of these assays might be subject to change during the course of the study (e.g. in case of assay re-optimization, qualification or standardization). In this case, this will be documented in the clinical study report.

Anti-PD antibodies

Anti-PD antibodies will be determined using a validated ELISA assay developed by GSK Biologicals. Concentration of specific anti-PD antibodies will be determined, using in-house made reference serum. The technical cut-off of the assay is 153 EU/mL.

Anti-PE antibodies

Anti-PE antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PE antibodies will be determined, using in-house made reference serum. The technical cut-off of the assay is ***16*** EU/mL. **(Amended 27 March 2019)**

Anti-PilA antibodies

Anti-PilA antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PilA antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ***8*** EU/mL. **(Amended 27 March 2019)**

Anti-UspA2 antibodies

Anti-UspA2 antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-UspA2 antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ***28*** EU/mL. **(Amended 27 March 2019)**

Cell-mediated immunity

CMI assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described in Table 11.

The ICS staining assay will be used to assess CMI responses, using an adaptation of previously described methods [Moris, 2011]. After PBMC stimulation with the relevant antigens, the frequency of $CD4^+$ and/or $CD8^+$ T-cells expressing selected set of cytokines (such as IL-2, IL-13, IL-17, IFN-γ, TNF-α and CD40L) or selected combination of cytokines will be evaluated by flow cytometry.

APPENDIX B CLINICAL LABORATORIES

Table 25 GSK Biologicals' laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart – Belgium
GSK Biological's Pre-clinical Laboratory, Rixensart	Rue de l'Institut, 89 - B-1330 Rixensart – Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium
GSK Biological's Pre-clinical Laboratory, Siena	Via Fiorentina, 1, 53100 Siena SI, Italy
GSK Vaccines GmbH Klinische Serologie, Clinical Laboratory Sciences	Gebaeude Z26 Emil-von-Behring Str. 76, Marburg 35041 - Germany

Table 26 Outsourced laboratories (Amended 27 March 2019)

Laboratory	Address
CEVAC - University of Gent	***De Pintelaan, 185 Gent, Belgium***
DDL Diagnostic Laboratory B.V.	***Visseringlaan 25, 2288 ER Rijswijk, The Netherlands***
Q^2 Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Q^2 Solutions Clinical Trials (UK)	The Alba Campus Rosebank Livingston West Lothian, EH54 7EG Scotland, UK

APPENDIX C MEDDRA PREFERRED TERMS FOR POTENTIAL IMMUNE MEDIATED DISEASES

Table 27 MedDRA preferred terms for potential immune mediated diseases

Event Category	Immune-Mediated Disorder	MedDRA PT
Neuroinflammatory disorders	Cranial nerve disorders	Anosmia
		IIIrd nerve paralysis
		IIIrd nerve paresis
		IVth nerve paralysis
		IVth nerve paresis
		Trigeminal palsy
		Trigeminal nerve paresis
		VIth nerve paralysis
		VIth nerve paresis
		Facial paralysis
		Facial paresis
		Acoustic neuritis
		Glossopharyngeal nerve paralysis
		Tongue paralysis
		Vagus nerve paralysis
		Vocal cord paralysis
		Vocal cord paresis
		XIth nerve paralysis
		Hypoglossal nerve paralysis
		Hypoglossal nerve paresis
		Bulbar palsy
		Oculofacial paralysis
		Neuritis cranial
		Cranial nerve disorder
		Paresis cranial nerve
		Cranial nerve paralysis
		Cranial nerve palsies multiple
	Optic neuritis	Optic neuritis
	Multiple sclerosis	Multiple sclerosis
		Radiologically isolated syndrome
		Primary progressive multiple sclerosis
		Progressive multiple sclerosis
		Marburg's variant multiple sclerosis
		Secondary progressive multiple sclerosis
		Multiple sclerosis relapse
		Multiple sclerosis relapse prophylaxis
		Progressive relapsing multiple sclerosis
		Relapsing-remitting multiple sclerosis
		Tumefactive multiple sclerosis

Event Category	Immune-Mediated Disorder	MedDRA PT
	Transverse myelitis	Myelitis transverse
		Myelitis
		Noninfectious myelitis
	Guillain-Barré syndrome	Guillain-Barré syndrome
		Miller Fisher syndrome
	Acute disseminated encephalomyelitis/demyelination (including site specific variants)	Demyelination
		Autoimmune demyelinating disease
		Clinically isolated syndrome
		Leukoencephalomyelitis
		Leukoencephalopathy
		Acute disseminated encephalomyelitis
		Acute haemorrhagic leukoencephalitis
		Concentric sclerosis
		Encephalitis periaxialis diffusa
		Neuromyelitis optica spectrum disorder
		Autoimmune encephalopathy
		Bickerstaff's encephalitis
		Noninfective encephalitis
		Encephalitis autoimmune
		Rasmussen encephalitis
		Encephalitis allergic
		Encephalitis brain stem
		Encephalitis haemorrhagic
		Encephalomyelitis
		Noninfective encephalomyelitis
		Encephalitis post immunisation
		Panencephalitis
		Encephalitis toxic
	Myasthenia gravis	Myasthenia gravis
		Myasthenia gravis crisis
		Ocular myasthenia
		Myasthenic Syndrome
	Immune-mediated peripheral neuropathies and plexopathies	Autoimmune neuropathy
		Neuritis
		Anti-myelin-associated glycoprotein associated polyneuropathy
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Lewis-Sumner syndrome
		Demyelinating polyneuropathy
		Polyneuropathy idiopathic progressive
		Multifocal motor neuropathy
		Acute motor-sensory axonal neuropathy
		Acute motor axonal neuropathy
		Cervical neuritis
		Mononeuritis
		Mononeuropathy multiplex
		Brachial plexopathy
		Radiculitis brachial

Event Category	Immune-Mediated Disorder	MedDRA PT
	Narcolepsy	Narcolepsy
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus
		SLE arthritis
		Cutaneous lupus erythematosus
		Acute cutaneous lupus erythematosus
		Chronic cutaneous lupus erythematosus
		Subacute cutaneous lupus erythematosus
		Lupus cystitis
		Lupus encephalitis
		Lupus endocarditis
		Lupus enteritis
		Lupus hepatitis
		Lupus myocarditis
		Lupus myositis
		Lupus nephritis
		Lupus pancreatitis
		Lupus pleurisy
		Lupus pneumonitis
		Lupus-like syndrome
		Neuropsychiatric lupus
		Central nervous system lupus
		Pericarditis lupus
		Peritonitis lupus
		Systemic lupus erythematosus rash
	Systemic Scleroderma	Scleroderma
		Scleroderma renal crisis
		Scleroderma associated digital ulcer
		Reynold's syndrome
		Systemic sclerosis pulmonary
		Systemic scleroderma
		CREST syndrome
	Muscular autoimmune disorders	Polymyalgia rheumatica
		Dermatomyositis
		Polymyositis
		Juvenile polymyositis
		Immune-mediated necrotising myopathy
		Antisynthetase syndrome
	Rheumatoid arthritis and associated conditions	Rheumatoid arthritis
		Autoimmune arthritis
		Laryngeal rheumatoid arthritis
		Rheumatoid lung
		Rheumatoid scleritis
		Rheumatic brain disease
		Rheumatoid neutrophilic dermatosis
		Rheumatoid nodule
		Juvenile idiopathic arthritis
		Cogan's syndrome
		Palindromic rheumatism
		Still's disease
	Spondyloarthropathies	Arthritis reactive

Event Category	Immune-Mediated Disorder	MedDRA PT
		Reiter's syndrome
		Ankylosing spondylitis
		Spondylitis
		Spondyloarthropathy
		Juvenile spondyloarthritis
		Enteropathic spondylitis
	Psoriatic arthropathy	Psoriatic arthropathy
		Juvenile psoriatic arthritis
	Relapsing polychondritis	Polychondritis
	Mixed connective tissue disease	Overlap syndrome
		Mixed connective tissue disease
	Gout	Gout
		Gouty arthritis
		Gouty tophus
Gastrointestinal disorders	Inflammatory Bowel disease	Crohn's disease
		Colitis ulcerative
		Colitis microscopic
		Autoimmune colitis
		Inflammatory bowel disease
		Arthritis enteropathic
		Proctitis ulcerative
	Autoimmune pancreatitis	Autoimmune pancreatitis
	Celiac disease	Coeliac disease
Liver disorders	Autoimmune hepatitis	Autoimmune hepatitis
	Primary biliary cirrhosis	Biliary cirrhosis primary
	Autoimmune cholangitis	Cholangitis sclerosing
Endocrine and Metabolic disorders	Autoimmune thyroid diseases	Autoimmune hypothyroidism
		Atrophic thyroiditis
		Autoimmune thyroiditis
		Silent thyroiditis
		Hashimoto's encephalopathy
		Hashitoxicosis
		Basedow's disease
		Marine Lenhart syndrome
		Autoimmune thyroid disorder
	Autoimmune endocrine disorder (NOS)	Autoimmune endocrine disorder
	Diabetes mellitus type I	Type 1 diabetes mellitus
		Fulminant type 1 diabetes mellitus
	Polyglandular autoimmune syndrome	Polyglandular autoimmune syndrome type I
		Polyglandular autoimmune syndrome type II
		Polyglandular autoimmune syndrome type III
	Autoimmune hypophysitis	Lymphocytic hypophysitis
	Addison's disease	Addison's disease

Event Category	Immune-Mediated Disorder	MedDRA PT
Skin disorders	Psoriasis	Psoriasis
	Vitiligo	Vitiligo
	Erythema nodosum	Erythema nodosum
	Alopecia areata	Alopecia areata
	lichen planus	Lichen planus
	Sweet's syndrome	Acute febrile neutrophilic dermatosis
	Autoimmune bullous skin diseases	Pemphigus
		Pemphigoid
		Dermatitis herpetiformis
		Autoimmune dermatitis
	Localised Scleroderma	Morphoea
Vasculitides	Vasculitis and vasculitides	Acute haemorrhagic oedema of infancy
		Administration site vasculitis
		Anti-neutrophil cytoplasmic antibody positive vasculitis
		Aortitis
		Application site vasculitis
		Arteritis
		Arteritis coronary
		Behcet's syndrome
		Capillaritis
		Cerebral arteritis
		Chronic pigmented purpura
		Cutaneous vasculitis
		Diffuse vasculitis
		Eosinophilic granulomatosis with polyangiitis
		Erythema induratum
		Granulomatosis with polyangiitis
		Haemorrhagic vasculitis
		Henoch-Schonlein purpura
		Henoch-Schonlein purpura nephritis
		Hypersensitivity vasculitis
		Injection site vasculitis
		Kawasaki's disease
		Langerhans' cell histiocytosis
		Lupus vasculitis
		MAGIC syndrome
		Microscopic polyangiitis
		Nodular vasculitis
		Ocular vasculitis
		Optic ischaemic neuropathy
		Optic neuropathy
		Polyarteritis nodosa
		Pulmonary vasculitis
		Renal arteritis
		Renal vasculitis
		Retinal vasculitis
		Rheumatoid vasculitis
		Segmented hyalinising vasculitis
		Takayasu's arteritis
		Temporal arteritis
		Thromboangiitis obliterans

Event Category	Immune-Mediated Disorder	MedDRA PT
		Urticarial vasculitis
		Vaccination site vasculitis
		Vascular purpura
		Vasculitic rash
		Vasculitic ulcer
		Vasculitis
		Vasculitis cerebral
		Vasculitis gastrointestinal
		Vasculitis necrotising
Other	Stevens-Johnson syndrome	Stevens-Johnson syndrome
		Erythema multiforme
		Toxic epidermal necrolysis
	Blood autoimmune disoders	Autoimmune anaemia
		Autoimmune haemolytic anaemia
		Warm type haemolytic anaemia
		Cold type haemolytic anaemia
		Coombs positive haemolytic anaemia
		Evans syndrome
		Immune thrombocytopenic purpura
		Thrombocytopenic purpura
		Thrombotic thrombocytopenic purpura
		Autoimmune aplastic anaemia
		Autoimmune neutropenia
		Autoimmune pancytopenia
		Antiphospholipid syndrome
		Pernicious anaemia
	Autoimmune glomerulonephritis	Glomerulonephritis rapidly progressive
		IgA nephropathy
		IgM nephropathy
		Glomerulonephritis membranous
		Glomerulonephritis membranoproliferative
		Mesangioproliferative glomerulonephritis
		Autoimmune nephritis
		Chronic autoimmune glomerulonephritis
		Tubulointerstitial nephritis and uveitis syndrome
	Ocular autoimmune diseases	Uveitis
		Ocular pemphigoid
		Autoimmune retinopathy
		Acute macular outer retinopathy
		Autoimmune uveitis
	Autoimmune heart disease	Autoimmune myocarditis
		Autoimmune pericarditis
	Sarcoidosis	Sarcoidosis
		Pulmonary sarcoidosis
		Neurosarcoidosis
		Cutaneous sarcoidosis
		Liver sarcoidosis

Event Category	Immune-Mediated Disorder	MedDRA PT
		Muscular sarcoidosis
		Ocular sarcoidosis
	Sjögren's syndrome	Sjogren's syndrome
	Idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis
		Idiopathic interstitial pneumonia
		Interstitial lung disease
		Pulmonary fibrosis
	Goodpasture's syndrome	Goodpasture's syndrome
	Raynaud's phenomenon	Raynaud's phenomenon

APPENDIX D AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
IND number	16531
EudraCT number	2017-000880-34
Amendment number:	Amendment 1
Amendment date:	30 November 2017
Co-ordinating author:	PPD, XPE Pharma & Science for GSK Biologicals

Rationale/background for changes:

- Removal of the ® and ™ symbols in the document and simplification of the copyright statement as per GSK Legal Global Trade Marks (LGTM) department's recommendation.
- The tertiary endpoint regarding 'biomarkers' has been adjusted as haematology is measured at baseline only and not throughout the study and thus cannot be considered a study endpoint.
- $CD8^+$ T cell component was removed from the secondary endpoint, but kept in the exploratory/tertiary endpoint. Previous clinical studies have shown that the investigational NTHi and NTHi-Mcat vaccines do not induce $CD8^+$ T cell responses. This was observed in all studies performed with the NTHi vaccine and seen in the interim analysis of NTHi Mcat-001 study.
- The definition of 'current smoker' has been updated to better clarify the time frame during which a subject who stopped smoking is still considered as 'current smoker'. A definition for 'Study Works' was also added to the glossary of terms.
- An exclusion criterion was updated to clarify that only subjects with clinically significant respiratory diseases other than COPD (e.g. clinically significant lung fibrosis, clinically significant pulmonary embolism) need to be excluded from study participation.

- Footnote a and b of the Study Procedures Table were rewritten to clarify when some study procedures of the Screening Visit needs to be repeated (i.e. in case Visit 1 was done more than 29 days after the Screening Visit and if the subject has any medical condition [e.g. fever] that prevents his/her participation in the study within 29 days of Screening Visit) and when the entire Screening Visit needs to be repeated (i.e. in case the subject had AECOPD before Visit 1 and only after subject was stable for 30 days). The footnote to the study design overview figure was adjusted in a similar way.
- A footnote was added to the study procedures table to explain that solicited (general/local) AEs will be collected up to Day 7 post-vaccination, but solicited AEs ongoing at Day 7 will be followed until resolution (for a maximum of 30 days). This was also added to Section 6.9.21.
- A scientific rationale for collecting race/ethnicity was added per country specific requirement for France (Section 6.9.5).
- Cut-off values for anti-PE, anti-PilA and anti-UspA2 antibody ELISAs were updated following the re-set up of the assays.
- The PCR assay for sputum samples was not designed to discriminate amongst *Haemophilus influenzae* (Hi) serotypes. Results from AERIS epidemiological study [Wilkinson, 2017] showed that more than 99% of these bacteria would be Non-Typeable *Haemophilus influenzae* (NTHi). Therefore, the protocol was updated to clarify that the presence of Hi bacteria in sputum during exacerbation will be used to determine AECOPD associated to NTHi.
- The list of potential immune mediated diseases (Table 19) was updated (effective June 30th 2017). A list of MedDRA preferred terms for potential immune mediated diseases was added as Appendix C.
- The FDA reference was removed from the intensity scale for redness/swelling and temperature as the reference did not reflect the correct cut-off values for the different intensities that will be used in this study.
- A definition for 'All enrolled set' was missing in the original protocol. Table and listings referring to this cohort will be prepared.
- The 87% confidence interval (CI) was removed from all secondary analyses. This confidence interval will only be maintained for the primary analysis because the 95% CIs are underpowered for this study. All other sensitivity analyses on different cohorts will be described using 95% CIs. As the primary objective will have both 87% and 95%, the sensitivity analyses can be interpreted with 95% CIs.
- 'According-to-Protocol' was replaced by 'Per-Protocol Set' as per current CDISC standard for cohorts for analysis.
- A Full-Analysis Set (FAS) that corresponds to an intent-to-treat analysis was added. The FAS will include all randomized subjects who will receive at least 1 vaccine administration and, as per intention-to-treat 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).

- Additional minor updates were based on the scientific and operational experience gained from current COPD studies.
- Correction of some typographical errors. Some sentences were also reworded or additions were made for clarity.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Contributing authors

- PPD (~~Oversight Statistician~~ ***Director Clinical Statistics***)
- PPD ~~(Aixial for GSK Biologicals)~~ (Clinical Trials Supply Manager)

Copyright statement

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LIST OF ABBREVIATIONS

~~ATP:~~	~~According to protocol~~
eCOA:	***Electronic Clinical Outcome Assessment***
FAS:	***Full-Analysis Set***
PPS:	***Per-protocol set***

GLOSSARY OF TERMS

Current smoker:	A person who is currently smoking or who stopped smoking within the past 6 months ***before study start***.
Protocol amendment:	***The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.***
Study Works:	***Secure electronic Clinical Outcome Assessment (eCOA) Web-Portal where reports are displayed to investigator staff showing data entered on the eCOA devices used by subjects (eDiary) and allowing the investigator staff to make decisions such as changing the eligibility status of the patient on the study.***

Section 1.1.1 Chronic obstructive pulmonary disease and acute exacerbations

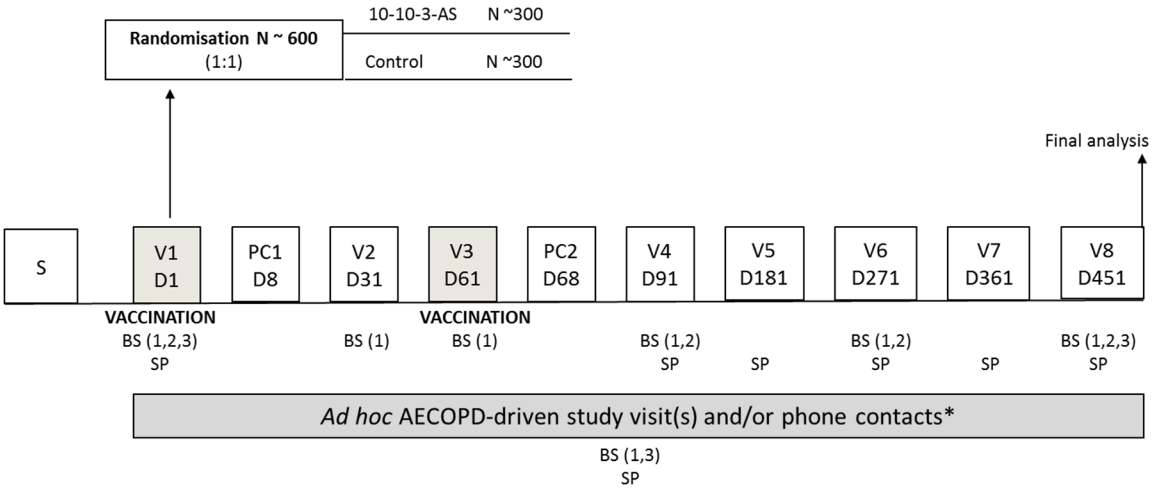
Table 1 Classification of severity of AECOPD

Grade	Intensity of medical intervention
Mild	Can be controlled with an increase in dosage of regular medications
Moderate	Requires treatment with systemic corticosteroids and/ or antibiotics
Severe	Requires hospitalisation*

In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment for AECOPD that would not have been appropriate in the physician's office or in an out-patient setting.

Section 3 Study design overview

Figure 2 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 ~~entire~~ Screening Visit need~~s~~ to be repeated ***within 7 days (see Table 6 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.

- **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***.

Section 4.1 Detection of AECOPD

- If the investigator concludes that the subject is not experiencing an AECOPD, this should be documented/ reported in the ~~eCRF~~ ***Study Works (Web portal)***. Please refer to study procedures manual (SPM) for more details on how to perform this.

The site must engage their best efforts to reach the patients, however, if the site does not succeed in contacting the patient, the reason should be recorded and an explanation given about what occurred. For example, the subject could be hospitalized or could visit a different physician (and in that case medical record***s*** should be obtained), or the subject is on holidays or not able to go ***to*** the site.

If an AECOPD occurs at the time of a scheduled study visit ~~and if the minimum 7 day interval between AECOPD visit and the scheduled study visit will result in a scheduled study visit falling outside of the allowed interval, the AECOPD visit can be scheduled within 7 days before the scheduled study visit.~~***, it should be handled and recorded as an AECOPD visit, with all relevant study procedures done during AECOPD-driven study visits performed and, if possible, the scheduled visit should be re-scheduled to a later date within the time window specified in the protocol.***

Some subjects may have been supplied with a prescription for antibiotics and/or steroids for treatment of AECOPD to use according to instructions provided by their physician in the event of an AECOPD occurring at a future date. During the course of this study, following an eDiary alert for potential AECOPD or other contact for potential AECOP, the investigator should make all possible efforts to ensure contact with the patient prior to the patient self-administering any antibiotics or steroids for their potential AECOPD. To manage situations where this prior contact cannot occur the investigator should use their clinical judgement.

Section 4.1.1. Date of onset and end date of AECOPD

Per inclusion criteria, the subject should be a stable COPD patient (i.e. a subject for whom the last episode of AECOPD is resolved for at least 30 days at the time of Screening). This effectively sets the baseline for evaluating the symptoms stated within the Anthonisen criteria (see Section 4.1). The date of onset of AECOPD is the first day (of at least 2 consecutive days) of worsening symptoms of COPD as determined by the investigator according to the Anthonisen criteria. For example, worsening of dyspnoea, sputum volume and sputum purulence is evaluated daily by the patient relative to this baseline. ***For an AECOPD confirmed by the investigator following an eDiary alert the onset date is considered to be the first day of 2 consecutive days that the patient enters symptoms meeting the Anthonisen criteria.*** Each day that there is no new symptom

effectively becomes the new baseline. Once the Anthonisen criteria are met, an eDairy alert is triggered. If the investigator determines this to be an AECOPD, that event is recorded via the eCRF. Subsequently, the investigator will follow the patient via phone contact (or clinic visit) at least every 2 weeks until resolution of this event.

Section 5.3 Exclusion criteria

- Diagnosed with a respiratory disorder other than COPD at time of enrolment (such as sarcoidosis, active tuberculosis, clinically significant bronchiectasis, ***clinically significant*** lung fibrosis, ***clinically significant*** pulmonary embolism, ***clinically significant*** pneumothorax, current diagnosis of asthma in the opinion of the investigator), or chest X-ray/ CT scan revealing evidence of clinically significant abnormalities not believed to be due to the presence of COPD. Subjects with allergic rhinitis do not need to be excluded and may be enrolled at the discretion of the investigator.
- Contraindication for spirometry testing (such as recent eye surgery, recent thoracic or abdominal surgery procedures, unstable cardiovascular status, recent myocardial ~~infection~~ ***infarction*** or pulmonary embolism).

Section 6.2.2.1 Randomisation of supplies

The randomisation of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centres /warehouse(s).

Section 6.2.2.2.1 Study group and treatment number allocation

The target will be to enrol approximately 600 eligible subjects who will be randomly assigned to two study groups in a (1: 1) ratio (approximately 300 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for age (40 - 59 years or 60 - 80 years), number of moderate/ severe AECOPD in the previous year (< 2 or ≥2**),** GOLD grade (GOLD 2, GOLD 3 or GOLD 4) and country. Minimisation factors will have equal weight in the minimisation algorithm**.**

Details on the minimisation algorithm are reported in the statistical analysis plan.

Section 6.5 outline of study procedures

Table 6 List of study procedures

Epoch	Epoch 001	Epoch 002									
Type of contact	Screening Visit [a]	Visit 1	Phone contact 1 [k]	Visit 2	Visit 3	Phone contact 2 [k]	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Timepoint	pre-Day 1	Day 1	Day 8	Day 31	Day 61	Day 68	Day 91	Day 181	Day 271	Day 361	Day 451
Sampling timepoint	Screening	Pre-Vacc 1	Post-Vacc 1		Pre-Vacc 2	Post-Vacc 2					
Informed consent	●										
Check inclusion/exclusion criteria	●	O									
Record of moderate and severe AECOPD within the previous year	O	●									
Check subject's COPD status		●	●	●	●	●	●	●	●	●	●
Record demographic data	●										
Record medical history, including significant comorbidities	O	●									
Vaccination history	O	●									
Smoking exposure history (ATS-DLD-78A questionnaire)	x										
Smoking status	●								●		●
Physical examination	●	O		O	O		O	O	O	O	O
Measure/record height and weight	●								O		●
Pre- and post-bronchodilator spirometry *(l)*	x [b]								x		x
Chest X-ray [d]	● [b]										
Pregnancy test [c]	● [b]	●			●						
Blood sampling:											
For humoral immunogenicity (~20 ml of blood)		●		●	●		●		●		●
For CMI (~40 ml of blood) [e]		●					●		●		●
For biomarkers, serum and plasma (~13 ml of blood)		●									●
For biomarker, haematology profile (~2 ml of blood)		●									
Sputum sampling [f]		●					●	●	●	●	●
Check contraindications to vaccination		O			O [g]						
Record pre-vaccination body temperature		●			●						
Study group and Treatment number allocation with randomisation		●			●						
Vaccination		●			●						

Epoch	Epoch 001	Epoch 002									
Type of contact	**Screening Visit** [a]	**Visit 1**	**Phone contact 1** [k]	**Visit 2**	**Visit 3**	**Phone contact 2** [k]	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Timepoint	**pre-Day 1**	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**	**Day 181**	**Day 271**	**Day 361**	**Day 451**
Sampling timepoint	**Screening**	**Pre-Vacc 1**	**Post-Vacc 1**		**Pre-Vacc 2**	**Post-Vacc 2**					
Train subject on the use of electronic Diary Card and assign electronic Diary Card to subject	O										
Distribute electronic Diary Card for recording of ***local and general AEs***, medication and vaccination, morning and evening ***COPD*** symptoms	O										
Collection of electronic Diary Card data [h]		x	x	x	x	x	x	x	x	x	x
Distribution of Subject Card	O										
Record AEs [i]		●	●	●	●	●	●	●	●	●	●
Record SAEs [i]	●[b]	●	●	●	●	●	●	●	●	●	●
Record pregnancies [i]		●	●	●	●	●	●	●	●	●	●
Record pIMDs [i]		●	●	●	●	●	●	●	●	●	●
Record concomitant medication/products and vaccination	O	●	●	●	●	●	●	●	●	●	●
Record intercurrent medical conditions			●	●	●	●	●	●	●	●	●
Return electronic Diary Card	O [j]	O [j]									O
HRQOL questionnaires:											
CAT	x								x		x
SGRQ-C	x								x		x
Healthcare Resource Utilisation		●	●	●	●	●	●	●	●	●	●
Screening conclusion	●										
Study Conclusion											●

D = Day; **Vacc** = vaccination. **PC** = Phone contact; **CAT** = COPD assessment test; **SGRQ-C** = St. George's Respiratory Questionnaire for COPD patients; **AECOPD** = Acute exacerbation of chronic obstructive pulmonary disease; **COPD** = chronic obstructive pulmonary disease; **CMI** = cell-mediated immunity; **AE** = adverse event; **SAE** = serious adverse event; **pIMDs** = potential immune mediated diseases; **HRQOL** = health-related quality of life.

● is used to indicate a study procedure that requires documentation in the individual eCRF; O is used to indicate a study procedure that does not require documentation in the individual eCRF; x is used to indicate a study procedure that does not require documentation in the individual eCRF as the data will be directly transferred from the provider to GSK.

[a] If needed, the Screening Visit***(s)*** can be done in more than ~~one~~ ***1*** day***. All screening procedures with the exception of eDiary training should be performed within 7 days from 1st screening visit***. The allowed maximum interval between ***1st*** Screening Visit and Visit 1 is 29 days. If a delay occurs for an eligible subject so that ~~the~~ interval exceeds 29 days, ~~the entire~~ ***some study procedures performed during*** Screening Visit***(s)*** need~~s~~ to be repeated ***(see footnote b)***. ***In case of AECOPD occurring before Visit 1, subjects***

should be treated outside the study according to standard practice. These subjects are considered screening failures. They will need to sign a new ICF, will receive a new subject number and will need to repeat the entire Screening Visit after they are stable for at least 30 days. The entire Screening Visit can only be repeated once. Once subject is determined as eligible, the eDiary for completion ~~from Day -14 to Day -1~~ will be given to the subject ***for a training period of maximum 14 days before Visit 1 (see Section 6.9.22).***

[b] ~~Screening failures could be due to the following reasons: 1) Visit 1 done more than 29 days after the Screening Visit. 2) In case of AECOPD occurring before Visit 1, subjects should be treated outside the study according to standard practice. These subjects can only continue in the study if the entire Screening Visit is repeated after they are stable for at least 30 days. 3)~~ ***Procedures indicated by this footnote need to be repeated*** If the subject has any medical condition (e.g. fever) that prevents his/her participation in the study within 29 days of Screening Visit. In ***that*** case ~~of screening failure~~, a re-Screening Visit ~~may~~ ***must*** be scheduled ***as soon as possible and no more than 7 days from Day 29 (Day 30 - Day 36)*** during which the procedures indicated by this footnote need to be repeated. ***Same as for the initial screening, the chest X-ray only has to be redone if no chest X-ray/ CT scan is available within the last 3 months.*** Data obtained during re-screening ***procedures*** should be entered in the eCRF.

[c] Pregnancy tests will be performed on ***all*** females of childbearing potential in case a chest X-ray will be performed. The pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive ***pregnancy*** test the chest X-ray should not be performed and the subject will be deemed not eligible for the study. Please also refer to Section 10.2.2. This pregnancy test should be repeated before vaccination at Visit 1 and Visit 3 (including those female subjects of childbearing potential who did not have a pregnancy test at screening because an X-ray/ CT scan was available within the last 3 months).

[d] Only if no chest X-ray/ CT scan available within the last 3 months.

[e] Only for subjects in the sub-cohort for CMI.

[f] Only if, in the opinion of the investigator, it is safe for the subject. Sputum samples can be either spontaneous or induced, as per investigator judgement.

[g] Refer to Section 7.5 for more details on study procedures for subjects meeting contraindications to subsequent vaccination before administration of vaccine Dose 2.

[h] The following information will be collected with the electronic Diary Card: COPD morning and evening symptoms (including EXACT-PRO questionnaire), smoking exposure history, local and general solicited AEs and Healthcare utilisation.

[i] Please refer to Table 20 for recording periods of local and general solicited AEs, AEs/SAEs leading to study withdrawal, SAEs, pregnancies and pIMDs. ***Solicited AEs will be collected up to Day 7 post- vaccination. Solicited AEs ongoing at Day 7 will be followed up until resolution (for a maximum of 30 Days). Unsolicited AEs will be collected for 30 days after each vaccination and thereafter only AEs leading to Withdrawal.***

[j] Only for Screening failures.

[k] The safety phone call at Day 8 and Day 68 can be performed by the (sub)-investigator or a medically trained delegate.

[l] ***If a good quality spirometry was not obtained, the spirometry can be repeated within 7 days, as per investigator medical judgement.***

Section 6.6 List of study procedures during AECOPD-driven study visits and phone contacts

In addition to the scheduled study visits, *ad hoc* AECOPD-driven study contacts will take place for each AECOPD occurring from first vaccination up to study conclusion. The procedures to be performed during these contacts are listed in Table 7.

In case of AECOPD occurring before Visit 1, subjects should be treated outside the study according to standard practice. These subjects ~~can only continue in the study if~~ ***are considered screening failures. They will need to sign a new ICF, will receive a new subject number and will need to repeat*** the entire Screening Visit ~~is repeated~~ after they are stable for at least 30 days.

Table 7 List of study procedures during AECOPD-driven study visits and phone contacts

Type of contact	AECOPD visit	End of AECOPD contact(s) (phone call[s] [7] and/ or visit[s])
Timepoint	**within 96 hours of onset symptoms**	**at least every 2 weeks from the AECOPD visit until AECOPD has resolved [1]**
Sampling timepoint	**AECOPD**	
Record date of visit	●	
Physical examination	O	O [2]
Chest X-ray [3]	●	
Pregnancy test [4]	●	
Confirm AECOPD and record its start date	●	
Blood sampling:		
For humoral immunogenicity (~5 ml of blood)	●	
For biomarkers, serum and plasma (~13 ml of blood)	●	
Sputum sampling [5]	●	
HRQOL questionnaire:		
CAT	x	
SGRQ-C	x	
Healthcare Resource Utilisation ***[8]***	●	●
Record AEs [6]	●	●
Record SAEs [6]	●	●
Record pregnancies [6]	●	●
Record pIMDs [6]	●	●
Record concomitant medication/products and vaccination	●	●
Record intercurrent medical conditions	●	●
Record AECOPD severity	O	●
Record AECOPD end date		●

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

x is used to indicate a study procedure that does not require documentation in the individual eCRF as the data will be directly transferred from the provider to GSK.

AECOPD = Acute exacerbation of chronic obstructive pulmonary disease; **HRQOL** = health-related quality of life; **CAT** = COPD assessment test; **SGRQ-C** = St. George's Respiratory Questionnaire for COPD patients; **AEs** = adverse events; **SAEs** = serious adverse events; **pIMDs** = potential immune mediated diseases.

[1] End of AECOPD phone calls/ visits should be scheduled at least every 2 weeks, until the AECOPD has resolved. Only the contact during which the end date of the AECOPD can be determined will be recorded in the eCRF as the end of the AECOPD contact. All intermediate contacts should be recorded on source documentation.

[2] Only applicable if the contact is a visit (not for phone calls).

[3] Only if clinically indicated to exclude another cause of worsening of symptoms (e.g. pneumonia).

[4] Pregnancy test will be performed on females of childbearing potential at each visit where a chest X-ray is performed. The pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive ***pregnancy*** test the chest X-ray should not be performed and the subject must not receive further study vaccinations. Please also refer to Section 10.2.2.

[5] Only if, in the opinion of the investigator, it is safe for the subject. Sputum samples can be either spontaneous or induced, as per investigator judgement. Self-collection of the sputum sample will be allowed in specific cases, where the first dose of antibiotics absolutely needs to be taken before an AECOPD visit can take place. As much as possible, the sputum sample collection should happen during the visit at investigator site. Self-collection is not allowed at scheduled visits when the subject should be in stable condition. See Section 6.9.15.2.

[6] Please refer to Table 20 for recording periods of local and general solicited AEs, unsolicited AEs, AEs/SAEs leading to study withdrawal, SAEs, pregnancies and pIMDs.

[7] The phone call to determine the end of AECOPD contact should be performed by the (sub)-investigator. Delegation to study staff should be agreed with the Sponsor.

[8] The AECOPD visit does not need to be recorded as a Healthcare Resource Utilisation.

Section 6.7 Concurrence of AECOPD-driven study visits and scheduled study visits

If an AECOPD occurs at the time of a scheduled study visit, it should be handled and recorded as an AECOPD visit, with all relevant study procedures ***done during AECOPD-driven study visits*** performed and, if possible, the scheduled visit should be re-scheduled to a later date within the time window specified in the protocol.

Section 6.8 Intervals between study visits

Whenever possible, the investigator should arrange study visits within the interval described in Table 8.

Table 8 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Scheduled study visits		
Screening Visit* → Visit 1	~~NA~~ ***14 days***	~~14~~ ***6*** - 29 days
Visit 1 → Phone contact 1	7 days	7 - 9 days
Visit 1 → Visit 2	30 days	30 - 45 days
Visit 1 → Visit 3	60 days	60 - 75 days [1]
Visit 3 → Phone contact 2	7 days	7 - 9 days
Visit 3 → Visit 4	30 days	30 - 45 days [1]
Visit 4 → Visit 5	90 days	90 - 120 days
Visit 4 → Visit 6	180 days	180 - 210 days
Visit 4 → Visit 7	270 days	270 - 300 days
Visit 4 → Visit 8	360 days	360 - 390 days
AECOPD-driven study visit(s) and/ or phone contacts		
Onset of AECOPD symptoms as recorded in the electronic Diary Card or confirmed by the subject → AECOPD Visit	NA	max 96 hours [2]
Interval between AECOPD Visit and scheduled study visit		
AECOPD visit → scheduled study visit	NA	min 7 days [3]

PC = phone contact; **AECOPD** = Acute exacerbation of chronic obstructive pulmonary disease; **NA** = Not applicable

[1] Subjects will not be eligible for inclusion in the ~~according-to-protocol (ATP) cohort~~ ***Per Protocol Set*** for analysis of immunogenicity if they make the study visit outside this interval.

[2] AECOPD visits will be scheduled as soon as possible after the onset of AECOPD symptoms as recorded in the electronic Diary Card or confirmed by the subject (maximum 96 hours after and, if applicable, preferably before starting treatment with antibiotics).

[3] If an AECOPD occurs at the time of a scheduled study visit, ~~and if the minimum 7 day interval between AECOPD visit and the scheduled study visit will result in a scheduled study visit falling outside of the allowed interval, the AECOPD visit can be scheduled within 7 days before the scheduled study visit.~~ ***it should be handled and recorded as an AECOPD visit, with all relevant study procedures done during AECOPD-driven study visits performed and, if possible, the scheduled visit should be re-scheduled to a later date within the time window specified in the protocol.***

**** In case of a re-Screening Visit, the visit must be scheduled as soon as possible and no more than 7 days from Day 29 (Day 30 - Day 36).***

Section 6.9.5 Collect demographic data

Record demographic data such as year of birth, sex, race and ethnicity in the subjects' eCRF.

Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez-Losada, 2009; Kollmann, 2013], have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g. genetics, metabolism, elimination), extrinsic factors (e.g. diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both race and ethnicity will be collected for all subjects participating in the NTHI MCAT-002 study.

Section 6.9.12 Pre- and post-bronchodilator spirometry

Spirometry will be performed ~~using techniques that meet published standards [NICE, 2010]~~ ***following the eResearchTechnology (ERT) instructions for use FlowScreen manual*** and following all safety requirements.

A good quality spirometry should be obtained, and will be confirmed by the spirometry provider. If a good quality spirometry was not obtained, the spirometry can be repeated within 7 days, as per investigator medical judgement. The data will be directly transferred from the provider to GSK Biologicals.

Section 6.9.15.1. Blood samples

Blood samples for humoral immunogenicity

A volume of approximately 20 mL of whole blood should be drawn from all subjects at Visit 1, Visit 2, Visit 3, Visit 4, Visit 6 and Visit 8. A volume of approximately 5 mL of whole blood should be drawn from all subjects at each AECOPD visit from first vaccination to study conclusion. After whole blood processing into serum, serum samples should be kept at ≤-20°C/-4°F ***or any temperature below*** until shipment.

Section 6.9.21. Recording of AEs, SAEs, pregnancies and pIMDs

- At Screening visit, electronic Diary Cards will be distributed to the subject. The subject will be instructed to measure and record the oral or axillary body temperature, and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days). ***Any solicited AE ongoing after Day 7 will be collected in the eDiary until resolution (for a maximum of 30 days).***

Section 6.9.24 Healthcare Resource Utilisation

Healthcare use for each COPD patient will be obtained through review of the subject's medical record (aided by subject self-reporting). Healthcare Resource Utilisation includes all unscheduled visits to a physician office, visits to urgent care, visits to emergency department, and hospitalizations. Healthcare use should be ~~entered~~ ***recorded in eDiary and reported*** in the eCRF ***at study visit***. Refer to the SPM for more details and guidance on recording of Healthcare Resource Utilisation.

Section 6.10.3. Laboratory assays

Table 10 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~~ ***25***	
	anti-PilA antibody				~~7~~ ***16***	
	anti-UspA2 IgG antibody				~~18~~ ***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.

** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Table 11 Cell-Mediated Immunity (CMI)

System	Component	Scale	Method	Unit	Laboratory
PBMCs	Specific $CD4^+$/~~$CD8^+$~~ T-cells	Quantitative	Flow cytometry ICS	Number of specific $CD4^+$/~~$CD8^+$~~-T-cells /10^6	GSK Biologicals* or GSK designated laboratory

PBMC = peripheral blood mononuclear cell; **ICS** = intracellular cytokine staining
* GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Additional vaccine antigen-specific $CD8^+$ T-cells data will be generated on peripheral blood mononuclear cells (PBMCs) in context of the specific $CD4^+$ T cell data generation by ICS.

The quality of sputum samples will be assessed at the investigator's institution and/ or at a laboratory designated by GSK Biologicals by Gram staining.

Identification and semi-quantitative assessment of **potential bacterial pathogens** will be performed on fresh sputum samples using **conventional bacteriological** methods at the investigator's institution and/ or at a laboratory designated by GSK Biologicals on a subset of subjects ***(50% of subjects)*** according to local laboratory procedures and agreed identification methods (potential pathogens including, but not necessarily limited to identification of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus* and *P. aeruginosa*).

Identification of potential bacterial pathogens (including, but not necessarily limited to, *H. influenzae, S. pneumoniae*, *M. catarrhalis, S. aureus*, *P. aeruginosa* and *Streptococcus pyogenes* [*S. pyogenes*]) and quantification (for *H. influenzae*, *S. pneumoniae, M. catarrhalis*) on frozen sputum samples will be performed at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals using qualified molecular methods such as multiplex ~~RT~~ ***real time*** PCR and/ or quantitative PCR (qPCR).

Further **bacterial characterisation** on frozen isolates of *H. influenzae* and/or *M. catarrhalis* will be done at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using either standard agglutination techniques or molecular tools, such as PCR, microarray serotyping and/or sequencing.

Viral pathogen identification (including, but not necessarily limited to, respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) on frozen sputum samples will be performed using multiplex PCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using ~~qualified~~ ***standardised and optimized*** procedures. In addition, viral pathogens (such as ***enterovirus/***rhinovirus) in frozen sputum samples will be quantified on all samples or a subset of samples (i.e. enterovirus***/rhinovirus***-positive sputum samples) using qPCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using ~~qualified~~ ***standardised and optimised*** procedures.

Table 12 Sputum assessments

Number of subjects	Group	Visit no.	Pathogen to identify	Type of sample	Method	Testing Laboratory
Quality assessment						
~600	Both	1 4 5 6 7 8 AECOPD visits	Please refer to SPM and/or Central Laboratory Manual for components tested	Fresh sputum	Gram staining	Investigator institution or GSK designated laboratory
Bacterial pathogen identification						
~300*	Both	1 4 5 6 7 8 AECOPD visits	*H. influenzae*	Fresh sputum	Standard bacteriological identification methods and ***semi-***quantitative ~~counts~~ ***assessment.***	Investigator institution or GSK designated laboratory
				Isolate	~~Sequencing~~	~~GSK Biologicals' ** or designated laboratory~~
					~~Hi vs *H. haemolyticus* discrimination~~***H. influenzae species confirmation and when possible Hi/NTHi differentiation*** by PCR	GSK Biologicals' ** or designated laboratory
			M. catarrhalis	Fresh sputum	Standard bacteriological identification methods and ***semi-***quantitative ~~counts~~ ***assessment***.	Investigator institution or GSK designated laboratory
				~~Isolate~~	~~Sequencing~~	~~GSK Biologicals' laboratory** or designated laboratory~~
			S. pneumoniae, P. aeruginosa, S. aureus, other potential pathogen	Fresh sputum	Standard bacteriological identification methods and ***semi-***quantitative ~~counts~~ ***assessment***.	Investigator institution or GSK designated laboratory

Number of subjects	Group	Visit no.	Pathogen to identify	Type of sample	Method	Testing Laboratory
~600	Both	1 4 5 6 7 8 AECOPD visits	*H. influenzae****,* *M. catarrhalis,* *S. pneumoniae*	Frozen sputum	Multiplex bacterial pathogen quantitative PCR assay	GSK Biologicals' ** or designated laboratory
			S. aureus, Group A streptococci, *P. aeruginosa*		Multiplex bacterial pathogen qualitative PCR assay	
Viral pathogen identification						
~600	Both	1 4 5 6 7 8 AECOPD visits	Respiratory viral pathogens (including respiratory syncytial virus, parainfluenza virus, enterovirus~~/~~***,*** rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus)	Frozen sputum	Multiplex viral pathogen qualitative PCR assay	GSK Biologicals** or designated laboratory
~600 or Subset (enterovirus***/rhinovirus*** positive samples)	Both		Rhinovirus	***Frozen sputum***	quantitative PCR assay	GSK Biologicals** or designated laboratory
Biomarker identification and quantification						
Patients not in culture subset*	Both	1 4 5 6 7 8 AECOPD visits	Inflammatory cytokines (such as TNF-α, IL-1, IL-8, IL-6)	Frozen sputum	Quantitative ELISA, multiplex CBA, ECL or PCR assays	GSK Biologicals** or designated laboratory

AECOPD = Acute exacerbation of chronic obstructive pulmonary syndrome; **SPM** = Study Procedures Manual; ***H. influenzae*** and **Hi** = *Haemophilus influenzae*; ***M. catarrhalis*** = *Moraxella catarrhalis*; ~~***H. haemolyticus*** = *Haemophilus haemolyticus*;~~ **PCR** = Polymerase Chain Reaction; ***S. pneumoniae*** = *Streptococcus pneumoniae*; ***S. aureus*** = *Staphylococcus aureus*; **TNF** = Tumor Necrosis Factor; **IL** = Interleukin; **ELISA** = Enzyme Linked Immunosorbant Assay; **CBA** = Cytometric bead assay; **ECL** = Electrochemiluminescence.

*Testing will only be performed on a subset of 50% of the subjects.

**GSK Biologicals laboratory refers to the pre-clinical team or the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

******The PCR assay can detect and quantify Hi in sputum samples. It can be assumed 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.***

Sputum samples might also be used for **assay development**, such as assays for diagnostic purposes or for microbiome analysis.

Additional testing on frozen sputum samples (such as, but not limited to, qPCR for other bacterial and/or viral pathogens, quantitative serotype-specific PCR, microarray typing, ***sequencing***, 16S RNA for microbiome analysis, presence (and/or concentration) of inflammatory cytokines) may be done during the study or after study completion, should these data be required for accurate interpretation of the study data and/ or for further research related to the investigational vaccine and/ or to respiratory diseases, should such test(s) become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Section 6.10.4.1 Immunological read-outs

Table 14 Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Vacc 1	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
				Fibrinogen, hsCRP, IP-10 and haematology profile*
		Sub-cohort for CMI	~120	Specific $CD4^+$/~~$CD8^+$~~ T-cell
Visit 2 (Day 31)	Post-Vacc 1	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
Visit 3 (Day 61)	Pre-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
Visit 4 (Day 91)	Post-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		Sub-cohort for CMI	~120	Specific $CD4^+$/~~$CD8^+$~~-T-cell
Visit 6 (Day 271)	Post-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		Sub-cohort for CMI	~120	Specific $CD4^+$/~~$CD8^+$~~-T-cell
Visit 8 (Day 451)	Post-Vacc 2	All enrolled subjects	~600	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
				Fibrinogen, hsCRP and IP-10
		Sub-cohort for CMI	~120	Specific $CD4^+$/~~$CD8^+$~~-T-cell
During each AECOPD visit from first vaccination to study conclusion		All enrolled subjects	-	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
				Fibrinogen, hsCRP and IP-10

hsCRP = high-sensitivity C-reactive protein, **CMI** = cell-mediated immunogenicity, **IP-10** = interferon gamma-induced protein 10.

*Including: WBC, neutrophils, eosinophils, lymphocytes, basophils, monocytes, RBC, haemoglobin and platelets.

Section 7.6 Concomitant medications/products and concomitant vaccination

At each study visit/contact, the investigator or delegate should question the subject about any medications/products taken and vaccinations received by the subject ***(including standard medication taken before first vaccination collected at Screening and/or at Visit 1)***. This includes the subject's COPD medication.

Section 9.1.5.1. Potential immune-mediated diseases

Table 19 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome • Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)
Vasculitides	**Blood disorders**	**Others**
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

~~Liver disorders~~	~~Gastrointestinal disorders~~	~~Endocrine disorders~~
• ~~Autoimmune hepatitis~~ • ~~Primary biliary cirrhosis~~ • ~~Primary sclerosing cholangitis~~ • ~~Autoimmune cholangitis~~	• ~~Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis~~ • ~~Celiac disease~~ • ~~Autoimmune pancreatitis~~	• ~~Autoimmune thyroiditis (including Hashimoto thyroiditis)~~ • ~~Grave's or Basedow's disease~~ • ~~Diabetes mellitus type I~~ • ~~Addison's disease~~ • ~~Polyglandular autoimmune syndrome~~ • ~~Autoimmune hypophysitis~~

Neuroinflammatory disorders	*Musculoskeletal disorders*	*Skin disorders*
• ***Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy).*** • ***Optic neuritis.*** • ***Multiple sclerosis.*** • ***Transverse myelitis.*** • ***Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.*** • ***Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.*** • ***Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.*** • ***Demyelinating peripheral neuropathies including:*** - ***Chronic inflammatory demyelinating polyneuropathy,*** - ***Multifocal motor neuropathy*** - ***Polyneuropathies associated with monoclonal gammopathy.*** • ***Narcolepsy.***	• ***Systemic lupus erythematosus and associated conditions*** • ***Systemic scleroderma (Systemic sclerosis), including:*** - ***Diffuse Scleroderma*** - ***CREST syndrome*** • ***Idiopathic inflammatory myopathies, including:*** - ***Dermatomyositis*** - ***Polymyositis*** • ***Anti-synthetase syndrome.*** • ***Rheumatoid Arthritis and associated conditions including:*** - ***Juvenile Idiopathic Arthritis*** - ***Still's disease.*** • ***Polymyalgia rheumatica.*** • ***Spondyloarthropathies, including:*** - ***Ankylosing Spondylitis,*** - ***Reactive Arthritis (Reiter's Syndrome),*** - ***Undifferentiated Spondyloarthritis,*** - ***Psoriatic Arthritis,*** - ***Enteropathic arthritis.*** • ***Relapsing Polychondritis.*** • ***Mixed Connective Tissue disorder.*** • ***Gout.***	• ***Psoriasis.*** • ***Vitiligo.*** • ***Erythema nodosum.*** • ***Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis).*** • ***Lichen planus.*** • ***Sweet's syndrome.*** • ***Localised Scleroderma (Morphoea).***

Vasculitis	*Blood disorders*	*Others*
• *Large vessels vasculitis including:* - *Giant Cell Arteritis (Temporal Arteritis),* - *Takayasu's Arteritis.* • *Medium sized and/or small vessels vasculitis including:* - *Polyarteritis nodosa,* - *Kawasaki's disease,* - *Microscopic Polyangiitis,* - *Wegener's Granulomatosis (granulomatosis with polyangiitis),* - *Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis),* - *Buerger's disease (thromboangiitis obliterans),* - *Necrotizing vasculitis (cutaneous or systemic),* - *anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified),* - *Henoch-Schonlein purpura (IgA vasculitis),* - *Behcet's syndrome,* - *Leukocytoclastic vasculitis.*	• *Autoimmune hemolytic anemia.* • *Autoimmune thrombocytopenia.* • *Antiphospholipid syndrome.* • *Pernicious anemia.* • *Autoimmune aplastic anemia.* • *Autoimmune neutropenia.* • *Autoimmune pancytopenia.*	• *Autoimmune glomerulonephritis including:* - *IgA nephropathy,* - *Glomerulonephritis rapidly progressive,* - *Membranous glomerulonephritis,* - *Membranoproliferative glomerulonephritis,* - *Mesangioproliferative glomerulonephritis.* - *Tubulointerstitial nephritis and uveitis syndrome.* • *Ocular autoimmune diseases including:* - *Autoimmune uveitis* - *Autoimmune retinitis.* • *Autoimmune myocarditis.* • *Sarcoidosis.* • *Stevens-Johnson syndrome.* • *Sjögren's syndrome.* • *Alopecia areata.* • *Idiopathic pulmonary fibrosis.* • *Goodpasture syndrome.* • *Raynaud's phenomenon.*
Liver disorders	*Gastrointestinal disorders*	*Endocrine disorders*
• *Autoimmune hepatitis.* • *Primary biliary cirrhosis.* • *Primary sclerosing cholangitis.* • *Autoimmune cholangitis.*	• *Inflammatory Bowel disease, including:* - *Crohn's disease,* - *Ulcerative colitis,* - *Microscopic colitis,* - *Ulcerative proctitis.* • *Celiac disease.* • *Autoimmune pancreatitis.*	• *Autoimmune thyroiditis (Hashimoto thyroiditis).* • *Grave's or Basedow's disease.* • *Diabetes mellitus type I.* • *Addison's disease.* • *Polyglandular autoimmune syndrome.* • *Autoimmune hypophysitis.*

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

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 ***as presented in Appendix C***. ***The list of PTs was created using MedDRA version 20.1.***

Section 9.3.3.2.1. Assessment of intensity

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals using ~~GSK Biologicals' standard~~ ***the following*** grading scale: ~~based on the US Food and Drug Administration (FDA) guidelines for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials" [FDA, 2007].~~

0 : < 20 mm diameter

1 : ≥ 20 mm to ≤ 50 mm diameter

2 : > 50 mm to ≤ 100 mm diameter

3 : > 100 mm diameter

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

0 : < 37.5°C

1 : 37.5°C to 3~~8.0~~***7.9***°C

2 : 38.~~1~~***0***°C to 3~~9.0~~***8.9***°C

3: ~~>~~≥ 39.0°C

Section 11.2 Secondary endpoints
Immunogenicity and CMI:

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.

Section 11.3 Tertiary endpoint
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 ~~and haematology profile at Visit 1~~.

Section 11.5.1 All enrolled set

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

Section 11.5.4 Per-protocol *set* for analysis of immunogenicity

The ~~according to protocol (ATP)~~ ***Per-protocol set (PPS)*** ~~cohort~~ for immunogenicity 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, as specified in Table 8.
- Who received the study vaccines according to protocol procedures.
- Who did not receive a concomitant medication/ product leading to elimination from the ~~ATP~~ ***PPS*** (per-protocol) analysis for immunogenicity (see Section 7.6.2) up to the 1 month post-Dose 2 visit (Day 91).
- Who did not present an intercurrent medical condition leading to elimination from the ~~ATP~~ ***PPS*** analysis for immunogenicity (see Section 7.7), up to the 1 month post-Dose 2 visit (Day 91).
- Who complied with the blood sample timings as specified in Table 8, at the 1 month post-Dose 2 visit (Day 91).
- For whom post-vaccination immunogenicity results are available for at least 1 assay.

Section 11.5.5 Per-protocol *set* for analysis of efficacy

The ~~ATP~~ ***PPS*** ~~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, as specified in Table 8.
- Who received the study vaccine according to protocol procedures.
- Not having received a medication/ product/ vaccine that may lead to elimination from the ~~ATP~~ ***PPS*** (per-protocol) analysis for efficacy (see Section 7.6.3).

In addition for the Bacteriological efficacy endpoints:

- ***For whom the sputum sample results are available.***

Section 11.5.6. Full Analysis set (FAS)

The FAS will include all randomized subjects who will receive at least 1 vaccine administration. As per intention-to-treat 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).

Section 11.6 Derived and transformed data

CMI

- The frequency of $CD4^+$ ~~or $CD8^+$~~ T-cells producing two or more markers (such as CD40 Ligand (CD40L), interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), upon in vitro stimulation with the antigen (induction condition) is presented per million of $CD4^+$ T ~~($CD8^+$T)~~ cells for the analysis and in percent 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 among IFN-γ, IL-2, IL-13, IL-17, TNF-α and/or CD40L, upon in vitro stimulation with the antigen (induction condition) minus the frequency of $CD4^+$ ~~or $CD8^+$~~ T-cells producing at least 2 cytokines upon in vitro stimulation in medium only (background condition).

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

$n^{2+}_{Induction}$ = Number of antigen-specific $CD4^+$/~~$CD8^+$~~ T-cells expressing two or more cytokines.

- The frequency of $CD4^+$ ~~or $CD8^+$~~ T-cells expressing a marker (such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α) upon *in vitro* stimulation with the antigen (induction condition) is presented per million of cells for the analysis and per hundred cells for the graphical representation.

Section 11.8 Analysis of efficacy

The primary analysis will be performed on the mTVC and repeated on the TVC ***and the FAS***. The primary analysis will also be repeated on the efficacy ATP (per-protocol) cohort if the percentage of vaccinated subjects excluded from the ATP cohort for efficacy is more than 5%.

Efficacy – Clinical Endpoint

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%~~ CI~~s~~, 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%~~ CI~~s~~:

- All-cause moderate and severe AECOPD (primary endpoint).
- All-cause, all-severity AECOPD.
- All-cause AECOPD, by severity.

For the primary analysis, the 95% CI will also be reported in order to evaluate the null hypothesis at 5% alpha level (2-side).

Incidence rates of AECOPD (any type) and VE, together ~~with 87% and~~ 95% CI~~s~~, will be computed for all study period (starting from day 1 until study termination) and at 3, 6, 9 and 12 months post-Dose 2, using the same model as for the primary.

A~~s~~ sensitivity analysis ***using*** a permutation test will be performed for the primary efficacy endpoint. ~~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).~~

Efficacy – Bacteriological Endpoint (PCR)

Similarly, VE in prevention of NTHi and/or Mcat associated AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year and ~~their 87% and~~ ***its*** 95% CI~~s~~ will be computed, with the following incidence rate:

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

The proportion of sputum samples with exact ~~87% and~~ 95% CI~~s~~ obtained at each visit (scheduled visits and AECOPD-driven visits) and positive for bacterial pathogens (overall and by bacterial pathogen) will be computed by group and overall. The exact CIs will be estimated assuming independence of bacterial results across sputum samples.

Incidence rates of AECOPD associated to NTHi and/or Mcat, and VE, together with ~~87% and~~ 95% CI~~s~~ will be evaluated for all study period (starting from Day 1 until study completion) and at 3, 6, 9 and 12 months post-Dose 2.

Efficacy – Bacteriological Endpoint (culture)

Same set of analyses, as in the bacteriological efficacy endpoint, will be performed in the subset of culture sputum data.

Incidence rates of AECOPD associated to NTHi and/or Mcat, and VE, together with ~~87% and~~ 95% CI~~s~~ will be evaluated for all study period (starting from Day 1 until study completion) and at 3, 6, 9 and 12 months post-Dose 2.

Bacteriological load

The following will be performed in PCR and culture samples:

- Percentage of subjects with *H. influenzae* and *M. catarrhalis* in sputum before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451, per group.
- Relative abundance of *H. influenzae* and *M. catarralis* in sputum as measured by culture before first vaccination and at Day 91, Day 181, Day 271, Day 361 and Day 451 ***and at each AECOPD visit***, per group.

Section 11.9.3 Cell-mediated immune response

Cell-mediated immune response as part of secondary endpoints

CMI induced by the NTHi-Mcat candidate vaccine will be evaluated, presenting the frequencies of antigen-specific $CD4^+$ ~~/$CD8^+$~~T cells per 10^6 cells. The specific $CD4^+$~~/$CD8^+$~~T cells being identified as the $CD4^+$~~/$CD8^+$~~-T cells expressing at least 2 different cytokines/activation markers among CD40L, IL-2, TNF-α, IFN- γ, IL-13 and IL-17 upon *in vitro* stimulation. A descriptive statistics (Min, Q1, Median, Q3 & Max) will be reported for each group at Day 1, Day 91, Day 271 and Day 451.

Cell-mediated immune response as part of tertiary endpoints

CMI response as the frequencies of specific $CD4^+$~~/$CD8^+$~~T cells per 10^6 cells expressing any combination of cytokines/activation markers will be determined. In addition, the T helper profile of the specific T cell response in T helper 1, T helper 2 and T helper 17 based on the specific expression of respectively IFN-γ, IL-13 and IL-17 will be characterized. A descriptive statistics (Min, Q1, Median, Q3 & Max) will be reported for each group at Day 1, Day 91, Day 271 and Day 451.

Section 14 References

~~FDA, U.S. Department of Health and Human Services, Center for Biologics Evaluation and Research. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Version of September 2007.~~

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APPENDIX A LABORATORY ASSAYS

Humoral immunity

Serological assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described below and in Table 10. The cut-off and unit of these assays 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.

APPENDIX C MEDDRA PREFERRED TERMS FOR POTENTIAL IMMUNE MEDIATED DISEASES

Table 27 MedDRA preferred terms for potential immune mediated diseases

Event Category	*Immune-Mediated Disorder*	*MedDRA PT*
Neuroinflammatory disorders	*Cranial nerve disorders*	*Anosmia*
		IIIrd nerve paralysis
		IIIrd nerve paresis
		IVth nerve paralysis
		IVth nerve paresis
		Trigeminal palsy
		Trigeminal nerve paresis
		VIth nerve paralysis
		VIth nerve paresis
		Facial paralysis
		Facial paresis
		Acoustic neuritis
		Glossopharyngeal nerve paralysis
		Tongue paralysis
		Vagus nerve paralysis

Event Category	*Immune-Mediated Disorder*	*MedDRA PT*
		Vocal cord paralysis
		Vocal cord paresis
		XIth nerve paralysis
		Hypoglossal nerve paralysis
		Hypoglossal nerve paresis
		Bulbar palsy
		Oculofacial paralysis
		Neuritis cranial
		Cranial nerve disorder
		Paresis cranial nerve
		Cranial nerve paralysis
		Cranial nerve palsies multiple
	Optic neuritis	*Optic neuritis*
	Multiple sclerosis	*Multiple sclerosis*
		Radiologically isolated syndrome
		Primary progressive multiple sclerosis
		Progressive multiple sclerosis
		Marburg's variant multiple sclerosis
		Secondary progressive multiple sclerosis
		Multiple sclerosis relapse
		Multiple sclerosis relapse prophylaxis
		Progressive relapsing multiple sclerosis
		Relapsing-remitting multiple sclerosis
		Tumefactive multiple sclerosis
	Transverse myelitis	*Myelitis transverse*
		Myelitis
		Noninfectious myelitis
	Guillain-Barré syndrome	*Guillain-Barré syndrome*
		Miller Fisher syndrome
	Acute disseminated encephalomyelitis/demyelination (including site specific variants)	*Demyelination*
		Autoimmune demyelinating disease
		Clinically isolated syndrome
		Leukoencephalomyelitis
		Leukoencephalopathy
		Acute disseminated encephalomyelitis
		Acute haemorrhagic leukoencephalitis
		Concentric sclerosis
		Encephalitis periaxialis diffusa
		Neuromyelitis optica spectrum disorder
		Autoimmune encephalopathy
		Bickerstaff's encephalitis
		Noninfective encephalitis
		Encephalitis autoimmune
		Rasmussen encephalitis
		Encephalitis allergic
		Encephalitis brain stem
		Encephalitis haemorrhagic
		Encephalomyelitis
		Noninfective encephalomyelitis
		Encephalitis post immunisation
		Panencephalitis
		Encephalitis toxic
	Myasthenia gravis	*Myasthenia gravis*
		Myasthenia gravis crisis

Event Category	*Immune-Mediated Disorder*	*MedDRA PT*
		Ocular myasthenia
		Myasthenic Syndrome
	Immune-mediated peripheral neuropathies and plexopathies	*Autoimmune neuropathy*
		Neuritis
		Anti-myelin-associated glycoprotein associated polyneuropathy
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Lewis-Sumner syndrome
		Demyelinating polyneuropathy
		Polyneuropathy idiopathic progressive
		Multifocal motor neuropathy
		Acute motor-sensory axonal neuropathy
		Acute motor axonal neuropathy
		Cervical neuritis
		Mononeuritis
		Mononeuropathy multiplex
		Brachial plexopathy
		Radiculitis brachial
	Narcolepsy	*Narcolepsy*
Musculoskeletal disorders	*Systemic lupus erythematosus*	*Systemic lupus erythematosus*
		SLE arthritis
		Cutaneous lupus erythematosus
		Acute cutaneous lupus erythematosus
		Chronic cutaneous lupus erythematosus
		Subacute cutaneous lupus erythematosus
		Lupus cystitis
		Lupus encephalitis
		Lupus endocarditis
		Lupus enteritis
		Lupus hepatitis
		Lupus myocarditis
		Lupus myositis
		Lupus nephritis
		Lupus pancreatitis
		Lupus pleurisy
		Lupus pneumonitis
		Lupus-like syndrome
		Neuropsychiatric lupus
		Central nervous system lupus
		Pericarditis lupus
		Peritonitis lupus
		Systemic lupus erythematosus rash
	Systemic Scleroderma	*Scleroderma*
		Scleroderma renal crisis
		Scleroderma associated digital ulcer
		Reynold's syndrome
		Systemic sclerosis pulmonary
		Systemic scleroderma
		CREST syndrome
	Muscular autoimmune disorders	*Polymyalgia rheumatica*
		Dermatomyositis
		Polymyositis

Event Category	*Immune-Mediated Disorder*	*MedDRA PT*
		Juvenile polymyositis
		Immune-mediated necrotising myopathy
		Antisynthetase syndrome
	Rheumatoid arthritis and associated conditions	*Rheumatoid arthritis*
		Autoimmune arthritis
		Laryngeal rheumatoid arthritis
		Rheumatoid lung
		Rheumatoid scleritis
		Rheumatic brain disease
		Rheumatoid neutrophilic dermatosis
		Rheumatoid nodule
		Juvenile idiopathic arthritis
		Cogan's syndrome
		Palindromic rheumatism
		Still's disease
	Spondyloarthropathies	*Arthritis reactive*
		Reiter's syndrome
		Ankylosing spondylitis
		Spondylitis
		Spondyloarthropathy
		Juvenile spondyloarthritis
		Enteropathic spondylitis
	Psoriatic arthropathy	*Psoriatic arthropathy*
		Juvenile psoriatic arthritis
	Relapsing polychondritis	*Polychondritis*
	Mixed connective tissue disease	*Overlap syndrome*
		Mixed connective tissue disease
	Gout	*Gout*
		Gouty arthritis
		Gouty tophus
Gastrointestinal disorders	*Inflammatory Bowel disease*	*Crohn's disease*
		Colitis ulcerative
		Colitis microscopic
		Autoimmune colitis
		Inflammatory bowel disease
		Arthritis enteropathic
		Proctitis ulcerative
	Autoimmune pancreatitis	*Autoimmune pancreatitis*
	Celiac disease	*Coeliac disease*
Liver disorders	*Autoimmune hepatitis*	*Autoimmune hepatitis*
	Primary biliary cirrhosis	*Biliary cirrhosis primary*
	Autoimmune cholangitis	*Cholangitis sclerosing*
Endocrine and Metabolic disorders	*Autoimmune thyroid diseases*	*Autoimmune hypothyroidism*
		Atrophic thyroiditis
		Autoimmune thyroiditis
		Silent thyroiditis
		Hashimoto's encephalopathy
		Hashitoxicosis
		Basedow's disease
		Marine Lenhart syndrome
		Autoimmune thyroid disorder
	Autoimmune endocrine disorder (NOS)	*Autoimmune endocrine disorder*
	Diabetes mellitus type I	*Type 1 diabetes mellitus*
		Fulminant type 1 diabetes mellitus

Event Category	*Immune-Mediated Disorder*	*MedDRA PT*
	Polyglandular autoimmune syndrome	*Polyglandular autoimmune syndrome type I*
		Polyglandular autoimmune syndrome type II
		Polyglandular autoimmune syndrome type III
	Autoimmune hypophysitis	*Lymphocytic hypophysitis*
	Addison's disease	*Addison's disease*
Skin disorders	*Psoriasis*	*Psoriasis*
	Vitiligo	*Vitiligo*
	Erythema nodosum	*Erythema nodosum*
	Alopecia areata	*Alopecia areata*
	lichen planus	*Lichen planus*
	Sweet's syndrome	*Acute febrile neutrophilic dermatosis*
	Autoimmune bullous skin diseases	*Pemphigus*
		Pemphigoid
		Dermatitis herpetiformis
		Autoimmune dermatitis
	Localised Scleroderma	*Morphoea*
Vasculitides	*Vasculitis and vasculitides*	*Acute haemorrhagic oedema of infancy*
		Administration site vasculitis
		Anti-neutrophil cytoplasmic antibody positive vasculitis
		Aortitis
		Application site vasculitis
		Arteritis
		Arteritis coronary
		Behcet's syndrome
		Capillaritis
		Cerebral arteritis
		Chronic pigmented purpura
		Cutaneous vasculitis
		Diffuse vasculitis
		Eosinophilic granulomatosis with polyangiitis
		Erythema induratum
		Granulomatosis with polyangiitis
		Haemorrhagic vasculitis
		Henoch-Schonlein purpura
		Henoch-Schonlein purpura nephritis
		Hypersensitivity vasculitis
		Injection site vasculitis
		Kawasaki's disease
		Langerhans' cell histiocytosis
		Lupus vasculitis
		MAGIC syndrome
		Microscopic polyangiitis
		Nodular vasculitis
		Ocular vasculitis
		Optic ischaemic neuropathy
		Optic neuropathy
		Polyarteritis nodosa
		Pulmonary vasculitis
		Renal arteritis
		Renal vasculitis
		Retinal vasculitis
		Rheumatoid vasculitis
		Segmented hyalinising vasculitis

Event Category	*Immune-Mediated Disorder*	*MedDRA PT*
		Takayasu's arteritis
		Temporal arteritis
		Thromboangiitis obliterans
		Urticarial vasculitis
		Vaccination site vasculitis
		Vascular purpura
		Vasculitic rash
		Vasculitic ulcer
		Vasculitis
		Vasculitis cerebral
		Vasculitis gastrointestinal
		Vasculitis necrotising
Other	*Stevens-Johnson syndrome*	*Stevens-Johnson syndrome*
		Erythema multiforme
		Toxic epidermal necrolysis
	Blood autoimmune disoders	*Autoimmune anaemia*
		Autoimmune haemolytic anaemia
		Warm type haemolytic anaemia
		Cold type haemolytic anaemia
		Coombs positive haemolytic anaemia
		Evans syndrome
		Immune thrombocytopenic purpura
		Thrombocytopenic purpura
		Thrombotic thrombocytopenic purpura
		Autoimmune aplastic anaemia
		Autoimmune neutropenia
		Autoimmune pancytopenia
		Antiphospholipid syndrome
		Pernicious anaemia
	Autoimmune glomerulonephritis	*Glomerulonephritis rapidly progressive*
		IgA nephropathy
		IgM nephropathy
		Glomerulonephritis membranous
		Glomerulonephritis membranoproliferative
		Mesangioproliferative glomerulonephritis
		Autoimmune nephritis
		Chronic autoimmune glomerulonephritis
		Tubulointerstitial nephritis and uveitis syndrome
	Ocular autoimmune diseases	*Uveitis*
		Ocular pemphigoid
		Autoimmune retinopathy
		Acute macular outer retinopathy
		Autoimmune uveitis
	Autoimmune heart disease	*Autoimmune myocarditis*
		Autoimmune pericarditis
	Sarcoidosis	*Sarcoidosis*
		Pulmonary sarcoidosis
		Neurosarcoidosis
		Cutaneous sarcoidosis
		Liver sarcoidosis
		Muscular sarcoidosis
		Ocular sarcoidosis
	Sjögren's syndrome	*Sjogren's syndrome*

Event Category	*Immune-Mediated Disorder*	*MedDRA PT*
	Idiopathic pulmonary fibrosis	*Idiopathic pulmonary fibrosis*
		Idiopathic interstitial pneumonia
		Interstitial lung disease
		Pulmonary fibrosis
	Goodpasture's syndrome	*Goodpasture's syndrome*
	Raynaud's phenomenon	*Raynaud's phenomenon*

GlaxoSmithKline Biologicals Vaccines R&D **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
IND number	16531
EudraCT number	2017-000880-34
Administrative Change Number:	Administrative Change 1
Administrative Change date:	15 December 2017
Co-ordinating Author:	PPD, XPE Pharma & Science for GSK Biologicals

Rationale/Background for changes:

- The inconsistency between the changed cut-off values for anti-PE, anti-PilA and anti-UspA2 ELISA assays in Amendment 1 and the cut-off values mentioned in Appendix A (laboratory assays) was corrected in this Administrative Change.

Text has been added in the following sections, as indicated with *bold and italicized.*:

APPENDIX A LABORATORY ASSAYS

Anti-PE antibodies

Anti-PE antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PE antibodies will be determined, using in-house made reference serum. The technical cut-off of the assay is ~~8~~ ***25*** EU/mL.

Anti-PilA antibodies

Anti-PilA antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PilA antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~7~~ ***16*** EU/mL.

Anti-UspA2 antibodies

Anti-UspA2 antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-UspA2 antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~18~~ ***38*** EU/mL.

GlaxoSmithKline Biologicals

Vaccines R&D

Protocol Amendment 2

eTrack study number and Abbreviated Title	207489 (NTHI MCAT-002)
IND number	16531
EudraCT number	2017-000880-34
Amendment Number:	Amendment 2
Amendment date:	27 March 2019
Co-ordinating Author:	PPD, XPE Pharma & Science for GSK Biologicals

Rationale/Background for changes:

- The coordinating and contributing authors on (pages 1& 2) were updated to reflect the current team in this Amendment.
- Copyright statement (page 2), date updated in this Amendment.
- Glossary (pages 32 and 33), definitions were added for acquisition and apparition in this Amendment.
- The text in Section 1.4.1 (page 42) related to spirometry was aligned with the wording used in the informed consent form (ICF) in this Amendment.
- The text in Section 4.1.1 (page 50) was aligned with the wording used in the inclusion criteria in this Amendment.
- The text in footnote c of Table 6 (page 61) was amended to clarify that pregnancy tests will be performed in on all females of childbearing potential in this Amendment.
- The text in Section 6.9.14 (page 67) was aligned with the changes made to Footnote c for Table 6 in this Amendment.
- Clarification was provided in Section 6.9.21, Recording of AEs, SAEs, pregnancies and pIMDs (page 70) in this amendment (minor change to wording)
- Table 10 (page 75) the new ELISA cut-offs were added in this Amendment as there are now qualified assays.
- In Section 9.4.1 (page 100) text was added to clarify that AECOPD classified as SAE occurring within a defined time period should also be recorded in the eCRF as “AECOPD visit” or as “Missed AECOPD visit”
- Synopsis (page 11) referring to Section 2.3 Tertiary objectives (page 44), and Synopsis (page 17) referring to Section 11.3 Tertiary endpoints (page 110) has been updated to include the analyses of acquisition and apparition of bacteria in culture and PCR.

- Clarification of the correct process to report pIMDs during the study was included in Section 9.4.5 Reporting of pIMDs to GSK Biologicals (page 102) in this Amendment.
- Clarification was provided in Section 10.2.2 Subject (page 108) regarding the withdrawal procedure in this Amendment.
- In Section 11.3 (Tertiary Endpoints, page 110), "acquisition and apparition" was added to the endpoints.
- In Section 11.8, Analysis of Efficacy, Efficacy – Clinical (page 118) the text was modified to correct an inconsistency within the section, clarifying that all efficacy clinical endpoints will be computed with 95% confidence intervals with the exception of the primary clinical efficacy endpoint that will also be computed with 87% confidence interval. There will be no change in the interpretation of the analysis compared to the previous version of the Protocol.
- In Section 11.8, Analysis of Efficacy, Efficacy – Bacteriological Endpoint (PCR), (pages 119-120) text was added to clarify the timepoints for the analysis.
- In Section 11.8, Analysis of Efficacy, Efficacy – Bacteriological Endpoint (culture), (page 120) text was added to clarify the timepoints for the analysis.
- In Section 11.8 Analysis of Efficacy (page 120) a section was added regarding the definitions of acquisition and apparition and information regarding the analysis was added in this Amendment
- Appendix A Laboratory Assays (page 136), the new ELISA cut-offs were added in this Amendment as there are now qualified assays.
- Appendix B Clinical Laboratories, Table 26 (page 137) CEVAC and DDL added to the table of outsourced laboratories in this Amendment.
- Minor corrections; e.g. correction of minor typographical and formatting errors were made for clarity in Section 4.1.1 (from eDiaries to eDiary), Section 6.7 (from SP to SPM), Section 9.1.3 (from eDiaries to eDiary), Section 11.4 (Table 23 and Table 24 [*et al* removed from footnote Keen *et al.* (2007) to Keen, 2007]), Sections 11.5.4 (Per protocol to per protocol), and 11.9.3 (from A descriptive statistics to Descriptive statistics).

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Coordinating authors, page 1

- PPD ***(Amendment 2 onward)*** (XPE Pharma & Science for GSK Biologicals)

Contributing authors, page 2

- PPD ***(Senior Clinical Research & Development Lead)*** PPD ***(Amendment 2 onward) (Clinical Research & Development Lead)***

- PPD (Lead Statistician)
- PPD (Director Clinical Statistics)
- PPD ***(Amendment 2 onward) (Study Statistician)***
- PPD ***(Amendment 2 onward)*** (Study Delivery Leads)
- PPD (CLS Clinical Read-out Team Leader)
- PPD (CLS Study manager)
- PPD ***(Amendment 2 onward)*** (Clinical Trials Supply Manager)
- PPD (Clinical Safety Representative)
- PPD (Oversight Data Manager)
- PPD (Study Data Manager)
- PPD ***(Amendment 2 onward)*** (Regulatory Affairs Representatives)

Copyright statement, page 2

- GSK Biologicals' Protocol DS v 15.0 ©2017-***2019*** GSK group of companies or its licensor

Synopsis, page 11

- 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.

Synopsis, page 17

- Occurrence (presence and absence)***, acquisition, apparition,*** 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.

<u>Sputum sample culture</u>:

Occurrence (presence and absence)***, acquisition, apparition,*** 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.

Glossary, pages 32 and 33

The following definitions were added to the Glossary:

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.***

Section 1.4.1, Data/rationale for risk, Spirometry, page 42

~~Spirometry can be in few cases~~ ***In a few cases spirometry has been*** associated with dizziness. Strong exhalation can cause increased pressure in chest, eyes or stomach. ***Occasionally after receiving the albuterol/salmeterol inhaler, a temporary sensation of "heart racing" and shakiness may be felt.***

Section 2.3 Tertiary objectives, page 44

- 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.

Section 4.1.1, page 49

Per inclusion criteria, the subject should be a stable COPD patient (i.e. a subject for whom the last episode of AECOPD is resolved for at least 30 days at the time of ***first vaccination***).

Table 6, Footnote c, page 61

Pregnancy tests will be performed on ***all*** females of childbearing potential ***at screening and prior to vaccination (Visit 1 and Visit 3). I***n case a chest X-ray will be performed (i.e. in subjects who do not have an X-ray / CT scan***)***. The pregnancy test should be carried out prior to the chest X-ray and if a subject has a positive ***pregnancy*** test the chest X-ray should not be performed and the subject will be deemed not eligible for the study. Please also refer to Section 10.2.2~~. This pregnancy test should be repeated before vaccination at Visit 1 and Visit 3 (including those female subjects of childbearing potential who did not have a pregnancy test at screening because an X-ray/ CT scan was available within the last 3 months).~~

Section 6.9.14 Pregnancy, Page 67

Female subjects of childbearing potential are to have a pregnancy test at Screening ***and prior to vaccination (Visit 1 and Visit 3)***. The study vaccine may only be administered if the pregnancy test is negative.

Table 10: Humoral Immunity (Antibody determination) , page 74

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~~ ***16***	
	anti-PilA antibody				~~16~~ ***8***	
	anti-UspA2 IgG antibody				~~38~~ ***28***	

Section 6.9.21, Recording of AEs, SAEs, pregnancies and pIMDs, page 70

- At Screening visit, electronic Diary Cards will be distributed to the subject. The subject will be instructed to measure and record the oral or axillary body temperature, and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days). Any solicited AE ongoing after Day 7 will be ~~collected~~ ***followed*** in the eDiary until resolution (for a maximum of 30 days).

Section 9.4.1 Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals, page 100

The following text was added to the section: ***AECOPD (Section 4) hat meet the criteria of a SAE (Section 9.1.3) that occur in the time period defined in Section 9.3 should also be recorded in eCRF as "AECOPD visit" or as "Missed AECOPD visit".***

Section 9.4.5. Reporting of pIMDs to GSK Biologicals, page 102

Once a ***new onset of a pIMD or exacerbation of a pre-existing*** pIMD is diagnosed (serious or non-serious) in a study subject, …

Section 10.2.2. Subject withdrawal from study vaccines, page 108

A subject withdrawn from the study vaccines may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity ***according to protocol procedure*** ~~planned in the study protocol~~.

Section 11.3 Tertiary endpoints, page 110

Sputum sample PC

- Occurrence (presence and absence)***, acquisition, apparition,*** 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)***, acquisition, apparition,*** 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.

Section 11.8, Analysis of Efficacy, Efficacy – Clinical Endpoint, page 118

Efficacy – Clinical Endpoint

The following incidence rates of AECOPD (any type) occurring from enrolment up to 1 month post-Dose 2 will be computed together with ~~87%~~***95%*** CI, 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%~~***95%*** CI**:**

- All-cause moderate and severe AECOPD (primary endpoint).
- All-cause, all-severity AECOPD.
- All-cause AECOPD, by severity.

~~For the primary endpoint, the 95% CI will also be reported in order to evaluate the null hypothesis at 5% alpha level (2-side).~~ ***For the primary endpoint, the 87% CI will also be reported in order to evaluate the null hypothesis at 13% alpha level (2-side). This objective will be considered a success if the lower limit of the 87% CI will be above 0%.***

Section 11.8, Analysis of Efficacy, Efficacy – Bacteriological Endpoint (PCR), pages 119-120

Incidence rates of AECOPD associated to NTHi and/or Mcat, and VE, together with 95% CI will be evaluated for ~~all study period (starting from Day 1 until study completion) and at 3, 6, 9 and 12 months post-Dose 2~~ the following time periods:

- At Month 3, 6, 9, 12, 15 from day 1 (cumulative)
- ***At 6 months follow up period (from 1 month post-Dose 2)***
- ***At 3 months follow up period (from 1 month post-Dose 2)***

Section 11.8, Analysis of Efficacy, Efficacy – Bacteriological Endpoint (culture), page 120:

Incidence rates of AECOPD associated to NTHi and/or Mcat, and VE, together with 95% CI will be evaluated for ~~all study period (starting from Day 1 until study completion) and at 3, 6, 9 and 12 months post-Dose 2~~ the following time periods:

- At Month 3, 6, 9, 12, 15 from day 1 (cumulative)
- ***At 6 months follow up period (from 1 month post-Dose 2)***
- ***At 3 months follow up period (from 1 month post-Dose 2)***

The model used will be the same as for the primary analysis. All above analyses will be performed in sputum samples using PCR.

Section 11.8, Analysis of Efficacy, page 120 (the following text was added):

Acquisition and apparition

The following definitions will be used:

- ***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 (NT)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 apparition for each subject from Day 1), by treatment groups.***

Appendix A Laboratory Assays, page 136

Anti-PE antibodies

Anti-PE antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PE antibodies will be determined, using in-house made reference serum. The technical cut-off of the assay is ~~25~~ ***16*** EU/mL.

Anti-PilA antibodies

Anti-PilA antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PilA antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~16~~ ***8*** EU/mL.

Anti-UspA2 antibodies

Anti-UspA2 antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-UspA2 antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~38~~ ***28*** EU/mL.

Appendix B Clinical Laboratories, *Table 26: Outsourced laboratories* (page 137)

Laboratory	Address
CEVAC - University of Gent	***De Pintelaan, 185 Gent, Belgium***
DDL Diagnostic Laboratory B.V.	***Visseringlaan 25, 2288 ER Rijswijk, The Netherlands***
Q^2 Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Q^2 Solutions Clinical Trials (UK)	The Alba Campus Rosebank Livingston West Lothian, EH54 7EG Scotland, UK