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

Primary Study vaccine	GlaxoSmithKline (GSK) Biologicals' investigational Non-typeable *Haemophilus influenzae* (NTHi) vaccine, containing 10 µg of PD, 10 µg of PE-PilA and the adjuvant $AS01_E$ (GSK2838504A)
Other Study vaccine	Placebo control
eTrack study number and Abbreviated Title	200157 (NTHI-004)
EudraCT number	2013-003062-13
Date of protocol	Final Version 2: 28 October 2013
Date of protocol amendment	Amendment 1 Final: 27 March 2014 Amendment 2 Final: 15 December 2014 Amendment 3 Final: 15 April 2016
Title	An observer-blind study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational vaccine GSK2838504A when administered to COPD patients
Detailed Title	A Phase II, randomised, observer-blind, placebo-controlled, multi-centre study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational vaccine GSK2838504A, when administered intramuscularly according to a 0, 2 month schedule to COPD patients aged 40 to 80 years
Co-ordinating author **(Amended 15 April 2016)**	PPD, PPD (XPE Pharma & Science for GSK Biologicals)

eTrack study number and Abbreviated Title	200157 (NTHI-004)
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Contributing authors (Amended 15 April 2016)	• PPD, PPD, Clinical Research & Development Lead • PPD, PPD, Lead Biostatistician • PPD, Project Biostatistician • PPD, Study Delivery Lead • PPD (Novellas Healthcare for GSK Biologicals), PPD, Study Delivery Manager • PPD, ***CLS Clinical Read-Out Team Leader*** • PPD and PPD, ***CLS Laboratory*** Study Managers • PPD, PPD, PPD, PPD and PPD, PPD Safety Representatives • PPD (Aixial Pharma for GSK Biologicals) and PPD, Study Data Manager • PPD, ***Project Data Manager*** • PPD, PPD, Global Regulatory Lead

GSK Biologicals' Protocol DS v 14.0

Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	200157 (NTHI-004)
EudraCT number	2013-003062-13
Date of protocol amendment	Amendment 3 Final:15 April 2016
Detailed Title	A Phase II, randomised, observer-blind, placebo-controlled, multi-centre study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational vaccine GSK2838504A, when administered intramuscularly according to a 0, 2 month schedule to COPD patients aged 40 to 80 years
Sponsor signatory (Amended 15 April 2016)	***Ashwani Kumar Arora,*** ***Clinical and Epidemiology Project Lead***
Signature	_____
Date	_____

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Protocol Amendment 3 Rationale

Amendment number:	Amendment 3

Rationale/background for changes:

- In compliance with ICH requirements, the protocol mentions that all results will be presented in an integrated report at the end of the study.
- Following re-development and re-validation of the anti-PD ELISA, a new cut-off was defined.
- Reference to the GSK Biologicals' Laval laboratory was removed, as this laboratory will not be used in the study. In addition, this laboratory is no longer part of GSK Biologicals' laboratories.
- Internal assay qualification procedures were revised and it was decided that the level of characterisation of the ELISA assays can be minimal (set-up level) for this study as immunogenicity data are descriptive. In consequence, the assays will be standardized but not qualified as stated in the original version.This change will not impact the validity of the results.
- A tertiary endpoint was added as the presence of viral pathogens in sputum will be examined as part of microbiome analysis.
- In order to see early effects of the vaccine on the microbiome, analysis on fresh sputum samples (culture results) will be done on all available data up to the data lock point of the interim analysis.
- In order to have a first look whether or not the investigational vaccine has an impact on AECOPD, AECOPD analyses will be done up to the data lock point of the interim analysis.
- Wording was added to clarify process for collection of sputum *H. influenzae* sweeps.
- Wording was updated in order to be aligned with the Statistical Ananlysis Plan.
- In addition, minor edits in other sections were made for clarification purposes.

Protocol Amendment 3 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' investigational vaccine 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 on-site 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, 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	200157 (NTHI-004)
EudraCT number	2013-003062-13
Date of protocol amendment	Amendment 3 Final:15 April 2016
Investigator name	
	_____
Signature	
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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 9.4.3.1.

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 II, randomised, observer-blind, placebo-controlled, multi-centre study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational vaccine GSK2838504A, when administered intramuscularly according to a 0, 2 month schedule to COPD patients aged 40 to 80 years
Indication	Active immunisation to reduce the frequency of Non-typeable *Haemophilus influenzae* (NTHi)-associated moderate and severe acute exacerbations (AECOPD) in COPD patients with a previous history of AECOPD
Rationale for the study and study design	**Rationale for the study** The purpose of this Phase II study, in which the investigational NTHi vaccine will be administered for the first time to moderate and severe COPD patients (*i.e.* GOLD grade 2 and 3), is to assess the vaccine's safety, reactogenicity and immunogenicity in this population, and to evaluate in an exploratory manner whether an NTHi vaccine can reduce the frequency of moderate and severe AECOPD associated with NTHi. Placebo will be used as a control. Both the investigational NTHi vaccine and the placebo will be given on top of the standard of care. **Rationale for the study design** • **Scheduled study visits**, during which the effect of immunisation against NTHi will be evaluated, will take place at pre-defined timepoints. In addition, *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. Besides evaluating the effect of vaccination against NTHi on AECOPD, the information obtained during these AECOPD-driven study contacts will help refining the case definition of AECOPD and of NTHi-associated AECOPD. • As the investigational vaccine will be administered for the first time to moderate and severe COPD patients, an **internal Safety Review Committee (iSRC)** will be appointed next to the existing project's Safety Review Team (SRT) and safety holding rules have been defined. Administration **vaccine Dose 1** will follow a **staggered** design, starting with vaccination of GOLD 2 subjects only. Administration of vaccine Dose 1 to GOLD 3 subjects will depend on the favourable outcome of an iSRC evaluation of safety data up to at least day 6 after vaccination from

about 20 GOLD 2 subjects (*i.e.* approximately 10 subjects/ group).

In addition, starting administration of **vaccine Dose 2** will for each GOLD grade depend on the favourable outcome of an iSRC evaluation of all available safety data.

Rationale for the use of placebo

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

Objectives

Primary

- To describe the safety and reactogenicity of the investigational vaccine.

Secondary

- To describe the humoral and cellular immunogenicity of the investigational vaccine.

Tertiary

- To explore the impact of the investigational vaccine on AECOPD.
- To explore the impact of the investigational vaccine on NTHi presence in sputum.
- To explore the impact of the investigational vaccine on health-related quality of life (HRQOL).
- To explore the impact of the investigational vaccine on lung function.
- To explore the impact of the investigational NTHi vaccine on exercise capacity.
- To describe selected biomarkers in stable COPD and during AECOPD.
- To collect blood and sputum samples for assay development, for disease diagnostic purpose, for lung microbiome analysis and/ or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.

Study design

- **Experimental design:** Phase II randomised, observer-blind, placebo-controlled, multi-centre study with 2 parallel groups.
- **Duration of the study:** for each subject enrolled, the study will last approximately 16 months from Visit 1 up to study end:
  - **Epoch 001**: starting at Screening and ending at study conclusion.
- **Study groups:**
  - **Group 10-AS01E:** approximately 70 subjects receiving 2 doses of the investigational NTHi vaccine.
  - **Group Control:** approximately 70 subjects receiving 2 doses of placebo.

Synopsis Table 1 Study groups and epoch foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
10-AS01E	~70	40 - 80 years	X
Control	~70	40 - 80 years	X

- **Control**: placebo control.
- **Vaccination schedule:** 0, 2 months (*i.e.* at Visit 1 [Day 0] and Visit 4 [Day 60]).

Synopsis Table 2 Study groups and treatments foreseen in the study

Treatment name	Vaccine/ product name	Study groups	
		10-AS01E	Control
10µgAg/ $AS01_E$	NTHi-10	X	
	AS01E		
Placebo	NaCl		X

- **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 or GOLD 3).

  All factors will have equal weight in the minimisation algorithm.

- **Blinding:** observer-blind.

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind

- **Sampling schedule:**
  - **Blood samples for safety assessment** (haematology/ biochemistry parameters) will be collected from all subjects at the Screening Visit (pre-Day 0), Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60), Visit 5 (Day 67), Visit 6 (Day 90), Visit 8 (Day 270) and at Visit 10 (Day 450).
  - **Blood samples for assessment of humoral immunogenicity** will be collected from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60), Visit 6 (Day 90), Visit 8 (Day 270) and at Visit 10 (Day 450).
  - **Blood samples for assessment of cell-mediated immunogenicity (CMI)** will be collected from all subjects in the CMI sub-cohort at Visit 1 (Day 0), Visit 6 (Day 90), Visit 8 (Day 270) and at Visit 10 (Day 450).
  - **Blood samples for biomarkers** will be collected from all subjects at Visit 1 (Day 0), Visit 10 (Day 450) and at each AECOPD visit from first vaccination to study conclusion.
  - **Blood samples for assessment of haematology** parameters will be collected at each AECOPD visit.
  - **Sputum samples** will be collected from all subjects at the Screening Visit (pre-Day 0), Visit 6 (Day 90), Visit 7 (Day 180), Visit 8 (Day 270), Visit 9 (Day 360), Visit 10 (Day 450) 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**.
  - Daily at bedtime throughout the study (including during AECOPD): **EXACT-PRO**.

- **HRQOL assessments:**
  - All subjects will be asked to complete the **COPD assessment test (CAT)** at the Screening Visit (pre-Day 0), Visit 8 (Day 270), Visit 10 (Day 450) 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 0), Visit 8 (Day 270) and at Visit 10 (Day 450).
  - All subjects will be asked to complete the **Medical Research Council Dyspnoea (mMRC) scale** at the Screening Visit (pre-Day 0), Visit 8 (Day 270), Visit 10 (Day 450) 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 0), Visit 8 (Day 270) and at Visit 10 (Day 450).
- **Exercise capacity:** all subjects will be asked to perform the 6-Minute Walk Test (6MWT) at the Screening Visit (pre-Day 0) and at Visit 10 (Day 450).
- **Type of study:** self-contained.
- **Data collection:** electronic Case Report Form (eCRF), electronic Diary Cards and SITEpro tablets.
- **Safety monitoring:** safety evaluations by the SRT (blinded) and by an iSRC (unblinded) will be performed.

Number of subjects

The targeted sample size is ~70 subjects/ group (*i.e.* 140 subjects in total).

Endpoints (Amended 15 April 2016)

Primary

- Occurrence of each solicited local adverse event (AE), during the 7-day follow-up period (*i.e.* day 0 - 6) following each vaccination, in all subjects.
- Occurrence of each solicited general AE, during the 7-day follow-up period (*i.e.* day 0 - 6) following each vaccination, in all subjects.
- Occurrence of any unsolicited AE, during the 30-day follow-up period (*i.e.* day 0 - 29) following each vaccination, in all subjects.

- Occurrence of each haematological/ biochemical laboratory abnormality at Day 0, Day 7, Day 30, Day 60, Day 67, Day 90, Day 270 and Day 450, in all subjects.
- Occurrence of any potential immune-mediated disease (pIMD) from first vaccination up to study conclusion, in all subjects.
- Occurrence of any serious adverse event (SAE) from first vaccination up to study conclusion, in all subjects.

Secondary

- Anti-PD, anti-PE and anti-PilA total IgG antibody concentrations as measured by ELISA, at Day 0, Day 30, Day 60, Day 90, Day 270 and at Day 450, in all subjects.
- NTHi-specific cell-mediated immune responses as measured by flow cytometry intracellular cytokine staining (ICS) (frequency of specific $CD4^+$/$CD8^+$ T-cells expressing two or more markers, such as IL-2, IL-13, IL-17, IFN-γ, TNF-α and CD40L), at Day 0, Day 90, Day 270 and at Day 450, in a sub-cohort of subjects.

Tertiary

- Number of cases of NTHi-associated moderate and severe AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Number of cases of NTHi-associated AECOPD (any severity), over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Number of cases of moderate and severe AECOPD (any cause), over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Number of cases of AECOPD (any cause, any severity), over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Time to first AECOPD, in all subjects.
- Assessment of EXACT-PRO score, daily at bedtime throughout the study, in all subjects.
- NTHi presence in sputum, at Screening, Day 90, Day 180, Day 270, Day 360 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.

- Assessment of *CAT* score, at Screening, Day 270 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.
- Assessment of SGRQ-C score, at Screening, Day 270 and Day 450, in all subjects.
- Assessment of mMRC scale, at Screening, Day 270 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.
- Occurrence of rescue medication use, over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Occurrence of healthcare use for AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Assessment of FEV_1% of predicted normal value at Screening, Day 270 and Day 450, in all subjects.
- Assessment of 6MWT score, at Screening and Day 450, in all subjects.
- Occurrence of selected biomarkers in a subset of blood samples, at Day 0 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.
- ***Presence of respiratory viral pathogens in sputum (including respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) at Screening, Day 90, Day 180, Day 270, Visit Day 360 and Day 450 and at each AECOPD visit from first vaccination to study conclusion, in all subjects.***

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LIST OF ABBREVIATIONS

6MWT	6-Minute Walk Test
AE	Adverse event
AECOPD	Acute exacerbation of COPD
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATP	According-to-protocol
CAT	COPD assessment test
CI	Confidence interval
CLS **(Amended 15 April 2016)**	***Clinical Laboratory Sciences***
CMI	Cell-mediated immunity
COPD	Chronic obstructive pulmonary disease
CRDL	Clinical Research & Development Lead
eCRF	Electronic case report form
EDD	Estimated date of delivery
EGA	Estimated gestational age
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
eTDF	Electronic temperature excursion decision form
EU	European Union
EXACT-PRO	EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome
FDA	Food and Drug Administration, United States
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
GMC	Geometric mean concentrations
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
H. influenzae	*Haemophilus influenzae*
HRQOL	Health-Related Quality of Life
ICF	Informed consent form

ICS	Intracellular cytokine staining
IEC	Independent ethics committee
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IHC	International Conference on Harmonisation
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional review board
iSRC	Internal safety review committee
LMP	Last menstrual period
MATEX	MATerial EXcellence
M. catarrhalis	*Moraxella catarrhalis*
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
mMRC scale	Modified Medical Research Council Dyspnoea scale
MPL	Monophosphoryl Lipid A
NTHi	Non-Typeable *Haemophilus influenzae*
PA	Posterior to anterior
P. aeruginosa	*Pseudomonas aeruginosa*
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Protein D
PE	Protein E
PI	Prescribing information
pIMD	Potential immune-mediated disease
PT	Preferred term
qPCR	Quantitative polymerase chain reaction
RDE	Remote data entry
SAE	Serious adverse event
S. aureus	*Staphylococcus aureus*
SBIR	Randomisation system on internet
SDV	Source document verification
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SmPC	Summary of product characteristics
SPM	Study procedures manual

S. pneumoniae	*Streptococcus pneumoniae*
S. pyogenes	*Streptococcus pyogenes*
SRT	Safety review team
STGG	Skim milk, tryptone, glucose, and glycerin transport medium
TNF-α	Tumour necrosis factor alpha
TVC	Total vaccinated cohort
UK	United Kingdom
ULN	Upper limit of the normal range
USA	United States of America
VE	Vaccine efficacy
VSMB	Vaccine safety monitoring board
WBC	white blood cells
WHO-ICD	World Health Organisation - international classification of diseases

GLOSSARY OF TERMS

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.
- Oral contraceptives, either combined or progestogen alone.
- Injectable progestogen.
- Implants of etenogestrel or levonorgestrel.
- Estrogenic 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).
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, 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.
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 (see Section 6.3 for details on observer-blinded studies).
Current smoker:	A person who is currently smoking or who stopped smoking within the past 6 months.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are 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 according-to-protocol (ATP) analysis (see Sections 7.6.2, 7.6.3 and 11.5 for details on criteria for evaluability).
Former smoker:	A person who stopped smoking for at least 6 months.

Immunological correlate of protection:	The defined humoral antibody 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/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference 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.
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 AEs 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 the primary outcome, whether the clinical trial 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.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. Note: Any change that falls under the definition of a protocol amendment (*e.g.* a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
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.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs 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.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects.
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.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
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, identified by a unique number, according to the study randomisation or treatment allocation.

Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or 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) is a disease characterised by persistent airflow obstruction which is not fully reversible and which is usually progressive in the long term. The airflow limitation in COPD patients can be classified into GOLD grades as shown in Table 1 [GOLD, 2013].

Table 1 Classification of severity of airflow limitation in COPD (based on post-bronchodilator FEV_1)

GOLD grade	In patients with FEV_1/ FVC < 0.70:
GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

The airflow limitation in COPD is associated with an enhanced and chronic inflammatory response to noxious particles and gases in the airways and the lungs. COPD results from a gene-environment interaction. 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, 2013]. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to risk factors and the changing age structure of the world's population.

The morbidity and mortality of COPD is substantially contributed to by 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 hospitalisation. Between 40 - 60% of medical expenditure for COPD is a direct consequence of AECOPD [Cazzola, 2008].

The lungs are known to be colonised with different strains of bacteria [Erb-Downward, 2011]. 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* (*M. catarrhalis*) (3-25%) and *Streptococcus pneumoniae* (*S. pneumoniae*) (4-9%) [Alamoudi, 2007; Bandi, 2003; Hutchinson, 2007; Ko, 2007; Larsen, 2009; Murphy, 2005; Papi, 2006; Sethi, 2002; Sethi, 2008].

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 2) [Wedzicha, 2007].

Table 2 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

1.1.2. Current management of AECOPD

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 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.

No vaccine is currently indicated for the prevention of AECOPD, even though flu 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 management of COPD.

1.1.3. GSK Biologicals' investigational NTHi vaccine

GlaxoSmithKline (GSK) Biologicals is developing a vaccine targeting NTHi in order to reduce the frequency of moderate and severe AECOPD in COPD patients with a previous history of AECOPD. The vaccine is intended to be administered on top of standard of care. The selected investigational vaccine consists out of 3 conserved surface proteins (protein D [PD], protein E [PE] and PilA; the latter 2 are included in the vaccine as a fusion protein named PE-PilA) adjuvanted with GSK's proprietary Adjuvant System $AS01_E$.

Refer to the current Investigator Brochure and its supplement for information regarding the pre-clinical and clinical studies and the potential risks and benefits of the investigational NTHi vaccine.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

The purpose of this Phase II study, in which the investigational NTHi vaccine will be administered for the first time to moderate and severe COPD patients, is to assess the vaccine's safety, reactogenicity and immunogenicity in this population, and to evaluate in an exploratory manner whether an NTHi vaccine can reduce the frequency of moderate

and severe AECOPD associated with NTHi. Placebo will be used as a control. Both the investigational NTHi vaccine and the placebo will be given on top of the standard of care.

1.2.2. Rationale for the study design

1.2.2.1. Scheduled study visits and AECOPD-driven study contacts

Scheduled study visits, during which the effect of immunisation against NTHi will be evaluated, will take place at pre-defined timepoints (see Figure 1).

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 AECOPD symptoms (maximum 96 hours after and, if applicable, preferably before starting treatment with antibiotics).
- Follow-up phone call(s) and/ or visits will take place to determine the end of the AECOPD. These contacts will take place at least every 2 weeks, until the AECOPD has resolved.

Besides evaluating the effect of vaccination against NTHi on AECOPD, the information obtained during these AECOPD-driven study contacts will help refining the case definition of AECOPD and of NTHi-associated AECOPD.

1.2.2.2. Safety overview and staggered vaccination

As the investigational vaccine will be administered for the first time to moderate and severe COPD patients, an **internal Safety Review Committee (iSRC)** will be appointed next to the existing project's Safety Review Team (SRT) and safety holding rules have been defined.

The iSRC will conduct *unblinded* reviews of all available safety data from the present study, including data on AECOPD (frequency, intensity and duration). Each safety evaluation by the iSRC will be preceded by a *blinded* safety review of the same safety data by the SRT.

Administration of **vaccine Dose 1** will follow a **staggered** design, starting with vaccination of GOLD 2 subjects only. Administration of vaccine Dose 1 to GOLD 3 subjects will depend on the favourable outcome of an iSRC evaluation of safety data up to at least day 6 after vaccination from about 20 GOLD 2 subjects (*i.e.* approximately 10 subjects/ group).

In addition, starting administration of **vaccine Dose 2** will for each GOLD grade depend on the favourable outcome of an iSRC evaluation of all available safety data.

Refer to Section 9.10 for more detailed information on safety monitoring and escalation of safety signals to GSK Biologicals' Vaccine Monitoring Board (VSMB).

1.2.3. Rationale for the use of placebo

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

1.3. Benefit: Risk assessment

Please refer to the current IB for the summary of potential risks and benefits of the NTHi investigational vaccine.

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

1.3.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
NTHi 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 (data from two studies using NTHi vaccines: NTHI-002 (non-adjuvanted formulations) and NTHI-003 (adjuvanted and non-adjuvanted formulations).	Close monitoring of potential immune-mediated diseases in clinical development programs using adjuvants systems. The potential risk of events of possible autoimmune aetiology to occur is mentioned in the Informed Consent Form (ICF).

1.3.2. Benefit Assessment

Benefits considerations include:

- Contribution to the process of developing of a vaccine against AECOPD.
- Medical evaluations/assessments associated with this study (i.e. physical examination, blood testing [haematology and biochemistry data], spirometry).

1.3.3. Overall Benefit : Risk Conclusion

Taking into account the measures taken to minimize risks to subjects participating in this study, the potential and/or known risks identified in association with the candidate NTHi 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 describe the safety and reactogenicity of the investigational vaccine.

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

2.2. Secondary objective

- To describe the humoral and cellular immunogenicity of the investigational vaccine.

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

2.3. Tertiary objectives

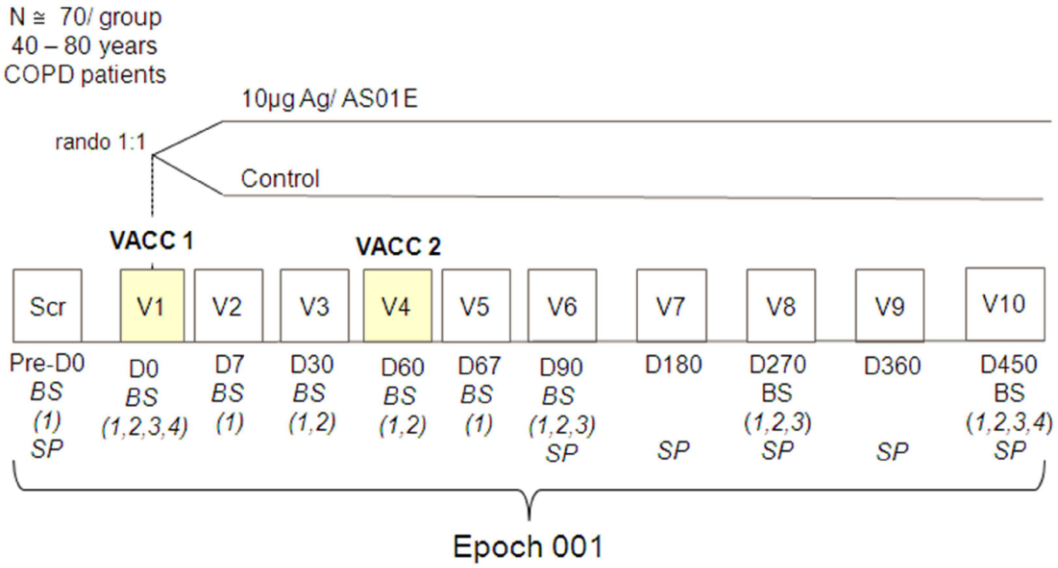
- To explore the impact of the investigational vaccine on AECOPD.
- To explore the impact of the investigational vaccine on NTHi presence in sputum.
- To explore the impact of the investigational vaccine on health-related quality of life (HRQOL).
- To explore the impact of the investigational vaccine on lung function.
- To explore the impact of the investigational NTHi vaccine on exercise capacity.
- To describe selected biomarkers in stable COPD and during AECOPD.
- To collect blood and sputum samples for assay development, for disease diagnostic purpose, for lung microbiome analysis and/ or for additional evaluation of the immune responses to the investigational vaccine and to other potential pathogens involved in AECOPD.

Refer to Section 11.3 for the definition of the tertiary endpoints.

3. STUDY DESIGN OVERVIEW

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

Figure 1 Study design overview



Scr = Screening; **V** = Visit; **D** = Day; **rando** = randomisation; **VACC**= vaccination; **BS(1)** = blood sample for safety; **BS(2) =** blood sample for humoral immunogenicity; **BS(3)** = blood sample for cell-mediated immunity (CMI); **BS(4)** = blood sample for biomarkers; **SP** = sputum sample

In addition to the scheduled study visits depicted above, *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 AECOPD symptoms (maximum 96 hours after and, if applicable, preferably before starting treatment with antibiotics). 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 has resolved.

- **Experimental design**: Phase II randomised, observer-blind, placebo-controlled, multi-centre study with 2 parallel groups.
- **Duration of the study**: for each subject enrolled, the study will last approximately 16 months from Visit 1 up to study end:
  - **Epoch 001**: starting at Screening and ending at study conclusion.
- **Study groups:**
  - **Group 10-AS01E:** approximately 70 subjects receiving 2 doses of the investigational NTHi vaccine.
  - **Group Control:** approximately 70 subjects receiving 2 doses of placebo.

Table 3 Study groups and epoch foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
10-AS01E	~70	40 - 80 years	X
Control	~70	40 - 80 years	X

- **Control**: placebo control.
- **Vaccination schedule:** 0, 2 months (*i.e.* at Visit 1 [Day 0] and Visit 4 [Day 60]).

Table 4 Study groups and treatments foreseen in the study

Treatment name	Vaccine/ product name	Study groups	
		10-AS01E	Control
10µgAg/ $AS01_E$	NTHi-10	X	
	AS01E		
Placebo	NaCl		X

- **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 or GOLD 3).

  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 5 Blinding of study epoch

Study Epochs	Blinding
Epoch 001	observer-blind

- **Sampling schedule**.
  - **Blood samples for safety assessment *** (haematology/ biochemistry parameters) will be collected from all subjects at the Screening Visit (pre-Day 0), Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60), Visit 5 (Day 67), Visit 6 (Day 90), Visit 8 (Day 270) and at Visit 10 (Day 450).

    * Additional blood sample(s) for safety assessment may be taken at the discretion of the investigator if deemed necessary.
  - **Blood samples for assessment of humoral immunogenicity** will be collected from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60), Visit 6 (Day 90), Visit 8 (Day 270) and at Visit 10 (Day 450).

- **Blood samples for assessment of cell-mediated immunogenicity (CMI)** will be collected from all subjects in the CMI sub-cohort at Visit 1 (Day 0), Visit 6 (Day 90), Visit 8 (Day 270) and at Visit 10 (Day 450).
- **Blood samples for biomarkers** will be collected from all subjects at Visit 1 (Day 0), Visit 10 (Day 450) and at each AECOPD visit from first vaccination to study conclusion.
- **Blood samples for assessment of haematology** parameters will be collected at each AECOPD visit.
- **Sputum samples** will be collected from all subjects at the Screening Visit (pre-Day 0), Visit 6 (Day 90), Visit 7 (Day 180), Visit 8 (Day 270), Visit 9 (Day 360), Visit 10 (Day 450) 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**.
  - Daily at bedtime throughout the study (including during AECOPD): **EXACT-PRO**.

- **HRQOL assessments:**
  - All subjects will be asked to complete the **COPD assessment test (CAT)** at the Screening Visit (pre-Day 0), Visit 8 (Day 270), Visit 10 (Day 450) 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 0), Visit 8 (Day 270) and at Visit 10 (Day 450).
  - All subjects will be asked to complete the **Medical Research Council Dyspnoea (mMRC) scale** at the Screening Visit (pre-Day 0), Visit 8 (Day 270), Visit 10 (Day 450) 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 0), Visit 8 (Day 270) and at Visit 10 (Day 450).

- **Exercise capacity:** all subjects will be asked to perform the 6-Minute Walk Test (6MWT) at the Screening Visit (pre-Day 0) and at Visit 10 (Day 450).

- **Type of study**: self-contained.

- **Data collection**: electronic Case Report Form (eCRF), electronic Diary Cards and SITEpro tablets.

- **Safety monitoring**: safety evaluations by the SRT (blinded) and by an iSRC (unblinded) will be performed. Refer to Section 9.10 for more detailed information on safety monitoring.

4. AECOPD

4.1. Detection of AECOPD

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

Note that:

- 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.
- Any symptom occurring on at least 5 consecutive days prior to a potential exacerbation will be discounted from the symptoms that define an exacerbation.

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 site staff contacts the subject to check whether an AECOPD visit is warranted. In addition, the site should pro-actively follow-up all data received via the electronic Diary Card and contact the subject whenever deemed necessary.

During the contact with the subject, the site 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).

For all potential AECOPD detected between first vaccination and study conclusion:

- If the site concludes that the subject is <u>not</u> experiencing an AECOPD, this should be documented/ reported.
- If the site concludes that the subject may be experiencing an AECOPD, 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 and, if applicable, preferably before starting treatment with antibiotics) *.

  ** 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.*

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

4.1.1. Date of onset and end date of AECOPD

The date of onset is the first day (of at least 2 consecutive days) of worsening symptoms of COPD.

The end date should be based on when the investigator determines that the AECOPD symptoms have resolved. In determining this end date, consideration should be given to symptoms recorded in the electronic Diary Card and subject assessment.

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

As the treatment given for an AECOPD might have an impact on relapse/ recurrence or time until the next AECOPD, guidance on how to preferably treat AECOPD is provided in Sections 4.2.1 and 4.2.2.

4.2.1. Guidelines for treatment with antibiotics

If there is evidence of respiratory infection that in the opinion of the investigator warrants the need for antibiotics the following guidelines are recommended:

- It is suggested to use an aminopenicillin, a macrolide or a tetracycline as initial empirical treatment for 7 days (taking into account guidance issued locally by infectious disease specialists or other relevant medical function).

- If first line antibiotic treatment fails and additional antibiotics are used, the total duration of antibiotic treatment should ideally be ≤ 30 days.

4.2.2. Guidelines for treatment with systemic corticosteroids

If in the opinion of the investigator the AECOPD is severe enough to warrant the need for systemic corticosteroids (with or without antibiotics) the following guidelines are recommended:

- It is suggested to use prednisolone 30 mg as initial empirical treatment for 7 days.
- The duration of treatment with systemic corticosteroids should ideally be ≤ 14 days.

4.3. Case definition NTHi-associated AECOPD

The case definition of **NTHi-associated AECOPD** has not been established yet. NTHi-association will be determined using sputum samples taken during AECOPD and could for instance be based on the presence of (NT)Hi (any), on (NT)Hi bacterial load or on the acquisition of a new strain of NTHi. The final case definition to be used in the analysis of this study will be built based on the data obtained in the on-going GSK Biologicals' study EPI-HIP-001 (114378) "*An epidemiology study to assess the contribution of bacterial and viral pathogens to AECOPD in adults and elderly between 40 and 85 years of age in the UK*".

An endpoint assessment/ adjudication committee may be appointed to review AECOPD.

5. STUDY COHORT

5.1. Number of subjects

The target is to enrol approximately 70 eligible COPD patients aged 40 to 80 years per study group (*i.e.* 140 subjects in total). Refer to Section 11.4 for a detailed description of the criteria used in the estimation of the sample size.

Approximately 40 subjects will be part of a **sub-cohort for CMI** analysis (~20 subjects/ group). An additional blood sample will be taken from these subjects at specified timepoints.

Table 6 Sub-cohort for CMI

Sub-cohort name	Description	Estimated number of subjects
Sub-cohort for CMI	At specific timepoints, an additional blood sample will be taken from these subjects for evaluation of the vaccine component-specific CMI responses.	~40 subjects (~ 20 subjects in each group)

5.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability 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).
- A male or female between, and including, 40 and 80 years of age at the time of the first vaccination.
- Written informed consent obtained from the subject.

- Confirmed diagnosis of COPD (based on post-bronchodilator spirometry) with forced expiratory volume in 1 second (FEV_1) over forced vital capacity (FVC) ratio (FEV_1/FVC) < 0.7, **AND** FEV_1 < 80% and ≥ 30% predicted (GOLD 2 and 3).
- 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 Screening.

  Refer to the Study Procedures Manual (SPM) for details on what is accepted as documented history of AECOPD. Refer to Table 2 for the definitions of moderate and severe AECOPD.
- Regular sputum producer.
- Capable to comply 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 current tubal ligation, hysterectomy, ovariectomy or post-menopause.

  Refer to the glossary of terms for the definition of 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.

  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 jeopardise the scientific integrity of the study, regulatory acceptability 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:

- 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).

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- 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.
- Previous vaccination with any vaccine containing NTHi antigens.
- 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.
- Chronic administration (defined as more than 14 days in total) of non-steroid immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose (*e.g.* methotrexate).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of immune-mediated disease other than COPD.

  Refer to Table 20 for a non-exhaustive list of potential immune-mediated diseases (pIMDs).
- Administration of systemic corticosteroids (prednisone ≥ 10 mg/day, or equivalent) within the 30 days before Screening.
  - Subjects who received systemic corticosteroids within this period may be enrolled at a later date if enrolment is still open.
- Administration of systemic antibiotics within the 30 days before Screening.
  - 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).
- Receiving oxygen therapy.
- Planned lung transplantation.
- Planned/ underwent lung resection surgery (*e.g.* lung volume reduction surgery or lobectomy).
- Diagnosis of α-1 antitrypsin deficiency as the underlying cause of COPD.
- Diagnosed with a respiratory disorder other than COPD (such as sarcoidosis, active tuberculosis, clinically significant bronchiectasis, lung fibrosis, pulmonary embolism, 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 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 infection or pulmonary embolism).
- Clinically significant* abnormality in haematology (haemoglobin, platelets or WBC) or biochemistry parameter (ALT, AST or creatinine), as per the judgement of the investigator.

  * As the study participants are COPD patients, various pre-existing haematological/ biochemical abnormalities might be detected. The investigator should use his/ her clinical judgement to decide which ones are clinically significant.
- Acute cardiac insufficiency.
- 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.
- Acute disease and/ or fever at the time of Screening.
  - Fever is defined as oral or axillary temperature ≥ 37.5°C. The preferred route for recording temperature in this study will be oral.
  - Subjects with acute disease and/ or fever at the time of Screening may be enrolled at a later date if enrolment is still open. Subjects with a minor illness without fever may be enrolled at the discretion of the investigator.
- 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 International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (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 informed consent must be obtained from each subject prior to participation in the study.

GSK Biologicals will prepare a model 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 of treatment

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 programme developed for use in Statistical Analysis

System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the drug depot.

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 140 eligible subjects who will be randomly assigned to the 2 study groups in a (1:1) ratio (approximately 70 subjects in each group).

Allocation of a subject to a study group at the investigator site will be performed using a centralised randomisation system on the 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) and GOLD grade (GOLD 2 or GOLD 3). All factors will have equal weight in the minimisation algorithm.

At Visit 1, before administration of vaccine Dose 1 to eligible subjects who signed and dated the ICF at the Screening Visit, the dedicated site staff 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 and his/ her GOLD grade, 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, refer to the SBIR user guide or the SPM for specific instructions.

6.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the dedicated study staff will access SBIR. Upon providing the subject identification number, 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 screen.

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

6.3. Method of blinding

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

Analysis

An analysis of immunogenicity and safety data up to Visit 6 (Day 90) will be done on as cleaned as possible data (please refer to Section 11.14.1 for more information). At this point, the GSK statistician (or delegates) of the project will be unblinded (*i.e.* will have access to the individual subject treatment assignment). The remaining GSK study personnel (excluding the iSRC members and their back-ups) will remain blinded (*i.e.* will not have access to the individual subject treatment assignment) until study end. It is possible however, due to the limited sample size, that unblinding occurs for a few subjects having a specific adverse event (AE) or serious adverse event (SAE) (*e.g.* an AE/ SAE occurring only in a single group). Therefore anyone having access to the analysis up to Day 90 could become unblinded regarding those specific cases.

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.

Refer to Section 9.10 for more information on safety monitoring and holding rules.

6.5. Outline of study procedures

6.5.1. Lists of study procedures during scheduled study visits

Table 7 List of study procedures during scheduled study visits

Epoch	Epoch 001										
Type of contact	**Screening [a b]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Timepoint	**pre-D0**	**D0**	**D7**	**D30**	**D60**	**D67**	**D90**	**D180**	**D270**	**D360**	**D450**
Sampling timepoint	**Screening**	**Pre-Vacc**	**Post-Vac 1**		**Pre-Vacc 2**	**Post-Vacc 2**					
Informed consent	●										
Check inclusion/exclusion criteria	● [b]	O									
Record history 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	x										
Smoking status	●								●		●
Physical examination	● [b]	O	O	O	O	O	O	O	O	O	O
Measure/ record height and weight	●								O		●
Pre- and post-bronchodilator spirometry	x								x		x
Chest X-ray [c]	●										
Urine pregnancy test [d]	● [b]	●			●						
Blood sampling:											
For safety assessment (~5.5 mL)	● [b]	●	●	●	●	●	●		●		●
For humoral immunogenicity (~25.5 mL)		●		●	●		●		●		●
For CMI (~40 mL) [e]		●					●		●		●
For biomarkers (~12.8 mL)		●									●
Sputum sampling [f]	●						●	●	●	●	●
Check contraindications to vaccination		O			O [g]						
Record pre-vaccination body temperature		●			●						
Treatment number allocation [h]		●			●						
Vaccination		●			●						
Distribute paper Diary Card for recording of vaccine reactogenicity		O	O		O	O					
Return paper Diary Card for recording of vaccine reactogenicity			O	O		O	O				

Epoch	Epoch 001										
Type of contact	**Screening [a b]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Timepoint	**pre-D0**	**D0**	**D7**	**D30**	**D60**	**D67**	**D90**	**D180**	**D270**	**D360**	**D450**
Sampling timepoint	**Screening**	**Pre-Vacc**	**Post-Vac 1**		**Pre-Vacc 2**	**Post-Vacc 2**					
Transcription of paper Diary Card for recording of vaccine reactogenicity			●	●		●	●				
Record AEs		●	●	●	●	●	●	●	●	●	●
Report SAEs	● [b]	●	●	●	●	●	●	●	●	●	●
Report pregnancies		●	●	●	●	●	●	●			
Distribute paper Diary Card for recording of medication	O										
Record concomitant medications/products and vaccinations	O	●	●	●	●	●	●	●	●	●	●
Return paper Diary Card for recording of medication											O
Record intercurrent medical conditions requiring medical attention		●	●	●	●	●	●	●	●	●	●
Train subject on the use of electronic Diary Card and assign electronic Diary Card to subject	O										
Return electronic Diary Card	O [i]	O [i]									O
6-minute walk test (6MWT)	●										●
HRQOL questionnaires:											
CAT	x								x		x
SGRQ-C	x								x		x
mMRC	x								x		x
Record healthcare use for past AECOPD (medical record review)		●	●	●	●	●	●	●	●	●	●
Screening conclusion	●										
Study conclusion											●

Note: the double-line borders indicate the statistical analyses which will be performed. The visits highlighted in grey are vaccination visits. **D** = Day; **Vacc** = vaccination.

● 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 can be done in more than one day (up to 7 days).

[b] For Screening failures due to reasons that are expected to be temporary (*e.g.* fever), a re-Screening visit may be scheduled during which the procedures indicated by this footnote need to be repeated. Data obtained during re-screening should be entered in the Screening Visit in the eCRF.

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

[d] Only for women of childbearing potential.

[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.

[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] Treatment number allocation with randomisation at Visit 1 (Day 0); treatment number allocation without randomisation at Visit 4 (Day 60).

[i] Only for Screening failures.

6.5.2. 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 8.

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.

Table 8 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] and/ or visit[s])
Timepoint	**within 96 hours of onset symptoms**	**at least every 2 weeks as of AECOPD visit until AECOPD has resolved [a]**
Sampling timepoint	**AECOPD**	
Record date of visit	●	
Physical examination	O	O [b]
Chest X-ray [c]	●	
Confirm AECOPD and record its start date	●	
Blood sampling:		
For biomarkers (~12.8 mL)	●	
For haematology assessment (~2 mL)	●	
Sputum sampling [d]	●	
HRQOL questionnaires:		
CAT	x	
mMRC	x	
Record healthcare use for AECOPD (medical record review)	O	●
Record AEs	●	●
Report SAEs	●	●
Report pregnancies [e]	●	●
Record concomitant medications/products and vaccinations	●	● [b]
Record intercurrent medical conditions requiring medical attention	●	●
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.
[a] 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.
[b] Only applicable if the contact is a visit (not for phone calls).
[c] Only if clinically indicated to exclude another cause of worsening of symptoms (*e.g.* pneumonia).
[d] Only if, in the opinion of the investigator, it is safe for the subject.
[e] Only for AECOPD visits from first vaccination up to 6 months post-Dose 2 (Day 240).

6.5.3. 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 performed and, if possible, the scheduled visit should be re-scheduled to a later date within the time window specified in the protocol. In consultation with GSK, only Visit 8 (Day 270) and Visit 10 (Day 450) may exceptionally be conducted outside of the allowed interval if necessary.

If an 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.

6.5.4. Intervals between study visits

Table 9 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Scheduled study visits		
Screening Visit completed → Visit 1	14 - 28 days [1]	14 - 28 days [1]
Visit 1 → Visit 2	7 days	7 - 9 days
Visit 1 → Visit 3	30 days	30 - 45 days
Visit 1 → Visit 4	60 days	60 - 75 days [2]
Visit 4 → Visit 5	7 days	7 - 9 days
Visit 4 → Visit 6	30 days	30 - 45 days [2]
Visit 6 → Visit 7	90 days	90 - 120 days
Visit 6 → Visit 8	180 days	180 - 210 days [3]
Visit 6 → Visit 9	270 days	270 - 300 days
Visit 6 → Visit 10	360 days	360 - 390 days [3]
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	-	max 96 hours [4]
Interval between AECOPD Visit and scheduled study visit		
AECOPD visit → scheduled study visit	-	min 7 days [5]

[1] Visit 1 should take place 14 - 28 days after Screening completed. If for an eligible subject, a delay occurs so that the interval between Screening completed and Visit 1 exceeds 28 days, the entire Screening Visit needs to be repeated.
[2] Subjects will not be eligible for inclusion in the according-to-protocol (ATP) cohort for analysis of immunogenicity if they make the study visit outside this interval.
[3] Subjects will not be eligible for inclusion in the ATP cohort for analysis of persistence of immunogenicity if they make the study visit outside this interval.
[4] 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).
[5] Scheduled study visits should not take place within 7 days of an AECOPD visit. If an AECOPD occurs at the time of a scheduled study visit so that this is not adhered to, the scheduled visit should be re-scheduled to a later date within the time window specified. In consultation with GSK, only Visit 10 (Day 450) may exceptionally be conducted outside of the allowed interval if necessary.

6.6. Detailed description of study procedures

6.6.1. Informed consent

The signed 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.

6.6.2. Check inclusion/ exclusion criteria

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

6.6.3. 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.

6.6.4. Check subject's COPD status

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

6.6.5. Record demographic data

Record demographic data such as year of birth, gender and geographic ancestry in the eCRF.

6.6.6. Medical history, including significant comorbidities

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 comorbidities 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.

6.6.7. 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]).

6.6.8. Smoking exposure history

The subject should self-complete the smoking history questionnaire (which is a shortened version of the ATS-DLD-78A questionnaire), which will be provided electronically via a SITEpro tablet. 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.

6.6.9. 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.

6.6.10. 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.

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.

6.6.11. Measure/ record height and weight

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

6.6.12. Pre- and post-bronchodilator spirometry

Pre- and post-bronchodilator spirometry should be performed during specified study visits as detailed in Table 7.

Only certified study staff can perform spirometry assessment.

Spirometry will be performed using techniques that meet published standards [NICE, 2010] and following all safety requirements.

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.

6.6.13. 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.

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.

6.6.14. Urine pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test at Screening and prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

6.6.15. 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.

6.6.15.1. Blood samples

Blood samples will be taken during specified study visits (scheduled visits and exacerbation visits) as detailed in Table 7 and Table 8.

Blood samples for safety assessment

For scheduled visits: a volume of approximately 5.5 mL of whole blood should be drawn from all subjects at each pre-defined timepoint (Table 10) and will be split and processed as follows:

- Approximately 2 mL of whole blood will be collected for haematology assessment. These samples will not be processed. They should be kept at room temperature and shipped on the day of collection.

- Approximately 3.5 mL of whole blood will be collected for biochemistry assessment and will be processed to serum. After processing, serum samples should be kept at room temperature and shipped on the day of collection.

(An) additional blood sample(s) for safety assessment may need to be drawn before administration of vaccine Dose 2, or during other study visits if deemed necessary by the investigator (see Table 10).

Blood samples for humoral immunogenicity

A volume of approximately 25.5 mL of whole blood should be drawn from all subjects at each pre-defined timepoint. After processing, serum samples should be kept at -20°C 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 each pre-defined timepoint. The samples should be kept at room temperature and will 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.

Blood samples for biomarkers

At Visit 1, Visit 10 and at each AECOPD visit: a volume of approximately 12.8 mL of whole blood should be drawn from all subjects and will be split and processed as follows:

- Approximately 5 mL of whole blood will be processed to serum. After processing:
  - An aliquot of serum should be kept at room temperature and shipped on the day of collection.
  - The remaining serum should be kept at -70/80°C until shipment.
- Approximately 6 mL of whole blood will be processed to plasma. After processing, plasma samples should be kept at -70/80°C until shipment.
- Approximately 1.8 mL of whole blood will be processed to plasma. After processing, plasma samples should be kept at -70/80°C until shipment.

At each AECOPD visit: a volume of approximately 2 mL of whole blood will be collected for haematology parameters from all subjects (Table 10). They should be kept at room temperature and shipped on the day of collection.

6.6.15.2. Sputum samples

Sputum samples will be collected during specified study visits (scheduled visits and exacerbation visits) as detailed in Table 7 and Table 8 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.

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

6.6.16. Check contraindications to vaccination

Contraindications to vaccination must be checked before each vaccination. 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.

6.6.17. Record pre-vaccination body temperature

The axillary or oral body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral. If the subject has fever (Fever is defined as oral or axillary temperature ≥ 37.5°C) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 9).

6.6.18. Treatment number allocation

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.

6.6.19. 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 9).

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.

6.6.20. Recording of adverse events, serious adverse events and pregnancies

Refer to Section 9.3 for procedures for the investigator to record AEs, SAEs and pregnancies. Refer to Section 9.4 for guidelines on how to submit pIMD, SAE and pregnancy reports to GSK Biologicals.

The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

Paper Diary Cards for recording of vaccine reactogenicity

- After each vaccination, **2** paper Diary Cards for recording of vaccine reactogenicity will be distributed to the subject:
  - A **1st** Diary Card will be distributed on the day of vaccination for daily recording of body temperature and of any solicited and unsolicited AEs from day 0 to 6 after each vaccination. The subject will be instructed to return the completed Diary Card to the study site at the next study visit (7 days post-vaccination).
  - A **2nd** Diary Card will be distributed at the 7 day post-vaccination visit for recording of any unsolicited AEs from day 7 to 29 after each vaccination. The subject will be instructed to return the completed Diary Card to the study site at the next study visit (30 days post-vaccination).
- Collect and verify completed Diary Cards during discussion with the subject during each 7-days post-vaccination visit and during each 30-day post-vaccination visit.
- Any unreturned Diary Cards will be sought from the subject through telephone call(s) or any other convenient procedure.
- The investigator will transcribe the collected information into the eCRF.

  Refer to the SPM for more details and guidance on Diary Card completion guidelines.

6.6.21. Record concomitant medications/ products and vaccinations

Paper Diary Card for recording of medication

At the Screening Visit, a paper medications Diary Card will be distributed to the subject:

- All vaccinations and medications (except for vitamins and dietary supplements) administered throughout the study period (including dose, unit, frequency and reason for use) should be recorded on this medication Diary Card.
- Subjects will be advised to bring all medications they are currently using during each of the study visits (including AECOPD-driven visits). At Screening, the medication Diary Card will be completed at the study site, with the help of the study staff. After that, the subject should update the Diary Card each time additional medication was taken, or a change to his/ her standard treatment was made.
- The medications Diary Cards will be reviewed with the subject at each study visit and a copy will be retained at the site.
- The investigator will transcribe the collected information into the eCRF.

  Refer to the SPM for more details and guidance on Diary Card completion guidelines.

6.6.22. Record intercurrent medical conditions requiring medical attention

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

6.6.23. 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.

6.6.24. 6-minute walk test

The subject should perform the supervised, standardised 6MWT at specified study visits as detailed in Table 7.

The result of the test should be recorded in the eCRF.

Refer to the SPM for more details and guidance on the 6MWT.

6.6.25. HRQOL questionnaires

The subject should self-complete the questionnaires on HRQOL (CAT, SGRQ-C and mMRC), which will be provided electronically via a SITEpro tablet, during specified study visits as detailed in Table 7 and Table 8.

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

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

6.6.26. Record healthcare use for AECOPD

Healthcare use for each AECOPD will be obtained through review of the subject's medical record (aided by subject self-reporting). Healthcare use for the AECOPD should be entered in the eCRF.

Refer to the SPM for more details and guidance on recording of healthcare use.

6.6.27. Confirm AECOPD and record its start date

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

6.6.28. Document AECOPD severity and end date

Indicate the severity and end date of each confirmed AECOPD in the eCRF. Refer to Table 2 for severity grading of AECOPD and to Section 4.1.1 for determination of end date.

6.6.29. 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 7).

6.6.30. Study conclusion

The investigator will:

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

6.7. Biological sample handling and analysis

Refer to the SPM and to the central laboratory 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).

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine and its constituents or the disease under study.
- Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/ or laboratories.

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.

6.7.1. Use of specified study materials

When materials are provided by GSK Biologicals ***or by the 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 according-to-protocol (ATP) analysis (See Section 11.5 for the definition of study cohorts/ data sets 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 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. **(Amended 15 April 2016)**

6.7.2. Biological samples

Table 10 Biological samples

Sample type	Quantity	Unit	Timepoints	Sub-cohort
Blood for safety assessment * (haematology and biochemistry)	~5.5	mL	• Screening Visit (pre-Day 0) • Visit 1 (Day 0) • Visit 2 (Day 7) • Visit 3 (Day 30) • Visit 4 (Day 60) • Visit 5 (Day 67) • Visit 6 (Day 90) • Visit 8 (Day 270) • Visit 10 (Day 450)	All screened subjects All enrolled subjects
Blood for humoral immunogenicity	~25.5	mL	• Visit 1 (Day 0) • Visit 3 (Day 30) • Visit 4 (Day 60) • Visit 6 (Day 90) • Visit 8 (Day 270) • Visit 10 (Day 450)	All enrolled subjects
Blood for CMI	~40	mL	• Visit 1 (Day 0) • Visit 6 (Day 90) • Visit 8 (Day 270) • Visit 10 (Day 450)	Sub-cohort for CMI
Blood for biomarkers	~12.8	mL	• Visit 1 (Day 0) • Visit 10 (Day 450) • During each AECOPD from first vaccination to study conclusion	All enrolled subjects
Blood for haematology parameters	~2.0	mL	• During each AECOPD	All enrolled subjects
Sputum	1	sample	• Screening Visit (pre-Day 0) • Visit 6 (Day 90) • Visit 7 (Day 180) • Visit 8 (Day 270) • Visit 9 (Day 360) • Visit 10 (Day 450) • During each AECOPD from first vaccination to study conclusion	All screened subjects All enrolled subjects

* Additional blood sample(s) for safety assessment may be taken at the discretion of the investigator if deemed necessary.

6.7.3. Laboratory assays

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

Haematology/ biochemistry

Haematology/ biochemistry assays for safety assessment will be performed in a central laboratory. Haematology assays on whole blood taken at AECOPD visits will be performed in the same central laboratory.

Table 11 Haematology and biochemistry

System	Discipline	Component	Method	Scale	Laboratory*
Whole blood	Haematology	Haemoglobin	commercial	Quantitative	Central laboratory
		Platelets	commercial	Quantitative	
		White Blood Cells (WBC) **	commercial	Quantitative	
Serum	Biochemistry	Alanine Aminotransferase (ALT)	commercial	Quantitative	Central laboratory
		Aspartate Aminotransferase (AST)	commercial	Quantitative	
		Creatinine	commercial	Quantitative	

*Refer to APPENDIX B for the laboratory address.
** Including WBC differential count.

Humoral antibody responses (Amended 15 April 2016)

Total IgG concentrations will be measured by ELISA at GSK Biologicals' laboratory. Standardised procedures will be used for all assays.

Table 12 Humoral Immunity (Antibody determination) (Amended 15 April 2016)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory*
Serum	Anti-PD	ELISA	In house	EL.U/mL	153	GSK Biologicals**
Serum	Anti-PE	ELISA	In house	EL.U/mL	8	GSK Biologicals**
Serum	Anti-PilA	ELISA	In house	EL.U/mL	7	GSK Biologicals**

EL.U/mL = ELISA unit per millilitre
*Refer to APPENDIX B for the laboratory addresses.
** GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences (CLS)*** in Rixensart, Belgium; Wavre, Belgium.

Serum and plasma samples might also be used for **development and/ or evaluation of other assays** to measure the immune response to the investigational NTHi vaccine components and/or to other NTHi antigens such as, but not limited to, bactericidal activity assay, assays measuring functional antibodies, immunochemistry assays for other immunoglobulin classes and/or for anti-IgG subclasses.

Additional testing on serum and plasma samples 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.

Cell-mediated immune responses

CMI assays will be performed at GSK Biologicals' laboratory using standardised and qualified procedures.

Table 13 Cell-Mediated Immunity

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**

PBMC = Peripheral Blood Mononuclear Cell; ICS = Intracellular Cytokine Staining
*Refer to APPENDIX B for the laboratory addresses.
** GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences (CLS)*** in Rixensart, Belgium; Wavre, Belgium. **(Amended 15 April 2016)**

Additional testing on Peripheral Blood Mononuclear Cells (PBMCs), such as, but not limited to, evaluation of NTHi-specific memory B-cells, 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 obtained during the processing of whole blood to obtain PBMCs will be stored for potential future analyses and/ or assay development purposes.

Microbiological assessments

Standard bacteriological culture will be performed on fresh sputum samples at the investigator's institution and/ or at a laboratory designated by GSK Biologicals. Quadrant assessment will be recorded from the primary culture plates and identification of **potential bacterial pathogens** will be performed according to local routine identification methods (potential pathogens including, but not necessarily limited to identification of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus* and *P. aeruginosa*). All results should be entered in the eCRF.

Further **characterisation of bacterial serotypes and/ or genotypes** on stored ***H. influenzae*** sweeps ***will*** be done at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using either standard agglutination techniques or molecular tools***, as microarray serotyping; considering that a "stored H. influenzae sweeps" is defined as the "harvest" of all microorganisms that have grown on the primary sputum culture plate (e.g. chocolate agar plate for H. influenzae growth) if at least one H. influenzae colony was observed on this plate.*** **(Amended 15 April 2016)**

Bacterial pathogen identification (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 stored sputum samples will be performed at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals using molecular methods such as multiplex ***RT*** PCR and/ or quantitative PCR (qPCR). **(Amended 15 April 2016)**

Viral pathogen identification (including, but not necessarily limited to, respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) on stored sputum samples will be performed using multiplex PCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using qualified procedures.
In addition, viral pathogens (such as rhinovirus) in stored sputum samples ***will*** be quantified ***on a subset of samples*** using qPCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using qualified procedures.
(Amended 15 April 2016)

Table 14 Microbiology (Amended 15 April 2016)

System	Component	Method	Scale	Laboratory*
Bacterial pathogen identification				
Fresh sputum †	Respiratory bacterial pathogens (including, but not limited to, *H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus* and *P. aeruginosa*)	standard bacteriological culture and standard identification methods including semi-quantitative culture	qualitative semi-quantitative	Investigator's institution and/ or laboratory designated by GSK Biologicals
Stored *H. influenzae* positive sputum and/ or stored sweep of positive *H. influenzae* culture plate	Characterisation of bacterial serotypes and/ or genotypes	Agglutination and/ or molecular tools ***(microarray serotyping)***	qualitative	GSK Biologicals** or designated laboratory
Stored sputum	Respiratory bacterial pathogens (including, but not limited to, *H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus, P. aeruginosa* and *S. pyogenes*)	Molecular methods such as multiplex PCR and/ or qPCR	qualitative quantitative	GSK Biologicals** or designated laboratory
Viral pathogen identification				
Stored sputum	Respiratory viral pathogens (including respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus)	Multiplex PCR	qualitative	GSK Biologicals** or designated laboratory
	Respiratory viral pathogens (such as rhinovirus)	qPCR	quantitative	GSK Biologicals** or designated laboratory

*Refer to APPENDIX B for the laboratory addresses.
** GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences (CLS)*** in Rixensart, Belgium; Wavre, Belgium.
† Bacterial culture of sputum stored in STGG (alternative storage) might be performed in a subset of samples at specific sites and/ or at GSK Biologicals' designated laboratory. More details will be provided in the SPM and associated documents.

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

Additional testing on stored sputum samples (such as, but not limited to, qPCR for other bacterial and/or viral pathogens, quantitative serotype-specific PCR, microarray typing, 16sRNA analysis) 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 COPD, should such test(s) become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Biomarkers

Table 15 Biomarkers

System	Component	Method	Scale	Laboratory*
Plasma	Fibrinogen	Commercial	Quantitative	Central laboratory
Serum	C-reactive protein (CRP)	Commercial	Quantitative	

*Refer to APPENDIX B for the laboratory address.

The presence of other selected biomarkers might be evaluated.

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.

6.7.4. Immunological correlates of protection

No generally accepted immunological correlate of protection has been established so far for the investigational NTHi 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 16 Study vaccines

Treatment name	Vaccine/ product name	Formulation	Presentation	Volume to be administered*	Number of doses
10µgAg/ $AS01_E$	NTHi-10 AS01E	PD=10µg; PE-PilA=10µg MPL=25µg; QS21=25µg; Liposomes	Freeze-dried antigens in monodose vial Liquid in monodose vial	0.5 mL	2
Placebo	NaCl	NaCl=150mM	Liquid in monodose vial	0.5 mL	2

*Refer to the SPM for the volume after reconstitution.

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 authorised 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 label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate electronic Temperature Excursion Decision Form (eTDF). 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 eTDF, but adequate actions must be taken to restore the +2 to +8°C label storage temperature conditions. The impacted IMPs 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 17 Dosage and administration

Type of contact (timepoint)	Volume to be administered	Study Group	Treatment name	Route	Site	Side
Visit 1 (Day 0)	0.5 mL	10-AS01E Control	10µgAg/ AS01E Placebo	IM	Deltoid	Non-dominant
Visit 4 (Day 60)	0.5 mL	10-AS01E Control	10µgAg/ AS01E Placebo	IM	Deltoid	Non-dominant

IM = intramuscular.

Refer to the SPM for detailed instructions on study vaccines administration.

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 20% 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 contraindications to administration of the investigational NTHi 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, or the subject may be 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 oral or axillary temperature ≥ 37.5°C. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness without fever can be administered all vaccines at the discretion of the investigator.

The following events constitute absolute contraindications to further administration of the investigational NTHi vaccine. If any of these events occur during the study, the subject must not receive vaccine Dose 2.

- 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).
- 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.
- Any other event which the investigator judges may put the safety of the subject at risk through vaccination.

For subjects meeting one of the above specified contraindications to subsequent vaccination before administration of vaccine Dose 2, the study visit at Day 67 (Visit 5) will be cancelled. These subjects will be invited to all other study visits as planned (including AECOPD-driven study visit[s] and/ or phone contact[s]) and will continue all study procedures as planned, with the exception of blood sampling for immunogenicity (humoral and CMI) and biomarkers and sputum sampling.

7.6. Concomitant medications/products and concomitant vaccination

Subjects will be advised to bring all medications they are currently using and their medications Diary Card to each study visit. During each visit, the medications Diary Card will be reviewed with the subject and a copy will be retained at the study site.

7.6.1. Recording of concomitant medications/products and concomitant vaccination

All vaccinations and medications (except for vitamins and dietary supplements) administered throughout the study period (including dose, unit, frequency and reason for use) must be recorded in the eCRF.

7.6.2. Concomitant medications/products and vaccines that may lead to the elimination of a subject from ATP analysis 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 ATP analysis for *immunogenicity***.**

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used at any time during the entire 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 or pneumococcal vaccines 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 summary of product characteristics (SmPC) or prescribing information (PI) 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 that may lead to the elimination of a subject from the ATP 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 will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP 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 ATP analyses for immunogenicity

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

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or if they become diagnosed with an immunological disorder.

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 he/ she manifest any signs or symptoms he/ she perceives 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

An 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), as well as unsolicited AEs occurring during a 30-day follow-up period after each vaccination (*i.e.* the day of vaccination an the 29 subsequent days), will be reported via paper Diary Cards for vaccine reactogenicity 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 18 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 19 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache

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

Note: temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not 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 (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 20.

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 20 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 • Scleroderma, including diffuse systemic form and CREST syndrome • Systemic sclerosis • Dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, • Juvenile chronic arthritis, (including Still's disease) • Polymyalgia rheumatic • 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) • Cutaneous lupus erythematosus • Alopecia areata • Lichen planus • Sweet's syndrome • Morphoea

Liver disorders	Gastrointestinal disorders	Metabolic diseases
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Crohn's disease • Ulcerative colitis • Ulcerative proctitis • Celiac disease	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease

Vasculitides	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 glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Uveitis • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

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.

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 vaccine but may continue other study procedures at the discretion of the investigator.

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 recognised 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 [EMA, 2006] 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 investigational vaccine/ product 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 vaccine must be recorded into appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

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

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

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at study conclusion. See Section 9.4 for instructions on reporting of SAEs.

In addition to the above-mentioned reporting requirements for SAEs 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. See Section 9.4 for instructions on reporting of SAEs.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end 6 months following administration of the last dose of study vaccine. See section 9.4 for instructions on reporting of pregnancies.

The time period for collecting and recording intercurrent medical conditions that require medical attention will begin at the first receipt of study vaccine and will end at study conclusion.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 21.

Table 21 Reporting periods for adverse events, serious adverse events and pregnancies

Visit	Screening Visit*	V1 Dose 1	6 days post-Dose 1	29 days post-Dose 1	V4 Dose 2	6 days post-Dose 2	29 days post-Dose 2	6 months post-Dose 2	Study Conclusion
Timepoint		D0	D6	D29	D60	D66	D89	D240	D450
Solicited local and general AEs									
Unsolicited AEs									
AEs/ SAEs leading to study withdrawal									
pIMDs									
SAEs									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									
Intercurrent medical conditions requiring medical									

V = Visit; **D** = Day.
* *I.e.* consent obtained.
The double-bordered lines indicate timings of vaccination.

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 21. 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 investigational vaccine/ product, 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 vaccine 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 22 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
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	Gastrointestinal symptoms 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

* Fever is defined as oral or axillary temperature ≥ 37.5°C. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/ swelling will be scored at GSK Biologicals as follows:

0 : ≤ 20 mm
1 : > 20 mm to ≤ 50 mm
2 : > 50 mm to ≤ 100 mm
3 : > 100 mm

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

0 : < 37.5 °C
1 : ≥ 37.5 °C to ≤ 38.5 °C
2 : > 38.5 °C to ≤ 39.5°C
3 : > 39.5°C

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 intensity 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 investigational vaccine/ product and the occurrence of each AE/ SAE. The investigator will use clinical judgement to determine the relationship. 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 investigational vaccine/ product will be considered and investigated. The investigator will also consult the Investigator Brochure and its supplement 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 SAE 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.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) 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 investigational vaccine?

YES	:	There is a reasonable possibility that the vaccine contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine 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 vaccine, 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).

9.3.3.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if he/ she received medical attention, defined as hospitalisation or an otherwise

unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

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

9.4.1. Prompt reporting of potential immune-mediated diseases, serious adverse events and pregnancies to GSK Biologicals

pIMDs that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 23, once the investigator becomes aware of the pIMD.

SAEs that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 23, 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 23, once the investigator becomes aware of the pregnancy.

Table 23 Timeframes for submitting potential immune-meditated disease, serious adverse event and pregnancy reports to GSK Biologicals

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

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed after the diagnosis is established and known to the investigator.

9.4.2. Reporting of pIMDs to GSK Biologicals

Once onset of a new 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 SAE report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. A field on the SAE report allows specifying that the event is a pIMD and whether it is serious or non-serious. The SAE 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.

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

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 SAE report WITHIN 24 HOURS. The SAE 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.

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

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

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

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

Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: GSK Biologicals Clinical Safety & Pharmacovigilance Fax: +PPD or +PPD

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. Updating of pIMD, SAE and pregnancy information after freezing of the subject's eCRF

When additional pIMD, SAE or pregnancy information is received after freezing of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Back-up Study Contact for Reporting SAEs (see Section 9.4.3.1) within the designated reporting time frames specified in Table 23.

9.4.6. 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 investigational vaccine/ product 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 23).

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.

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

The investigator will follow subjects with pIMDs (serious or non-serious), SAEs 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 SAE 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 SAE report, if applicable. Generally, the follow-up period does not 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 an AE should be recorded in 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 USA Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the investigational vaccine/ product, 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 study 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 internet-based 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 back-up) 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 SBIR).

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

GSK Biologicals' Contact Information for Emergency Unblinding **24/24 hour and 7/7 day availability**
GSK Biologicals' Central Safety Physician on-call: +PPD **GSK Biologicals' Central Safety Physician Back-up:** +PPD **Emergency Unblinding Documentation Form transmission** Fax: or +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.

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 meets on a regular basis. The SRT will inform the iSRC about any potential safety concern relevant to the study.

Before each iSRC safety evaluation in this study (see below), 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

As the investigational vaccine will be administered for the first time to moderate and severe COPD patients, an iSRC will be appointed next to the existing project's SRT and safety holding rules have been defined (see Table 24).

The iSRC will be authorised by GSK Biologicals' 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.

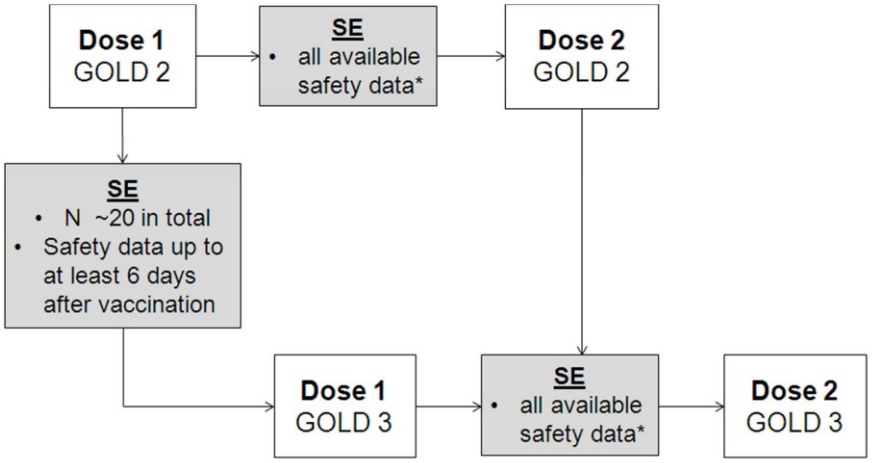
The iSRC will conduct *unblinded* reviews of all available safety data from the present study, including data on AECOPD (frequency, intensity and duration), while taking into account any other findings that could have an impact on the safety of the subjects, and will determine whether there is a safety 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.

Administration of **vaccine Dose 1** will follow a **staggered** design, starting with vaccination of GOLD 2 subjects only. Administration of vaccine Dose 1 to GOLD 3 subjects will depend on the favourable outcome of an iSRC evaluation of safety data up to at least day 6 after vaccination from about 20 GOLD 2 subjects (*i.e.* approximately 10 subjects/ group).

In addition, starting administration of **vaccine Dose 2** will for each GOLD grade depend on the favourable outcome of an iSRC evaluation of all available safety data.

In addition to the planned iSRC evaluations, *ad hoc* safety evaluations can take place if a safety concern is identified by an investigator (*e.g.* meeting of holding rules 1a-c) or by the SRT.

Figure 2 Overview of iSRC evaluation



SE = safety evaluation
* Safety evaluation on all available safety data, before the first subject needs to be administered vaccine Dose 2. In addition to the SEs depicted above, *ad hoc* safety evaluations can take place (for instance if holding rule 1a-c is met).

9.10.3. Study holding rules

As the investigational NTHi vaccine will be administered for the first time to moderate and severe COPD patients, study holding rules have been defined (see Table 24).

- **Holding rules 1a, 1b and 1c** will be monitored by the investigators on a continuous basis for as long as vaccination is on-going in the study. Meeting any of these holding rules will trigger a hold of vaccination irrespective of the number of subjects vaccinated.
- **Holding rules 2a, 2b and 2c** will be assessed by the iSRC during the safety evaluations.

Table 24 List of holding rules

Holding Rule	Event	Number/ percentage of subjects
1a	Death or any life-threatening **SAE**	≥ 1
1b	Any **withdrawal** from the study (by investigator or subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination	≥ 1
1c	Any local or general solicited AE leading to **hospitalisation**, or **body temperature > 40°C** that cannot reasonably be attributed to a cause other than vaccination, or **necrosis** at the injection site, within the 7-day (days 0-6) post-vaccination period	≥ 1
2a	Any **Grade 3 solicited local AE** lasting 48 hours or more in the investigational group, within the 7-day (day 0-6) post-vaccination period	≥ 25% **AND** ≥ 2 subjects/ group
2b	Any **Grade 3 general solicited AE** lasting 48 hours or more in the investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (day 0-6) post-vaccination period.	≥ 25% **AND** ≥ 2 subjects/ group
2c	Any **Grade 3 unsolicited** AE in the investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (day 0-6) post-vaccination period or Any ≥ **Grade 3** abnormality* in pre-specified **haematology or biochemistry laboratory parameter** in the investigational group, if it cannot reasonably be attributed to a cause other than vaccination, at day 7 post-vaccination.	≥ 25% **AND** ≥ 2 subjects/ group

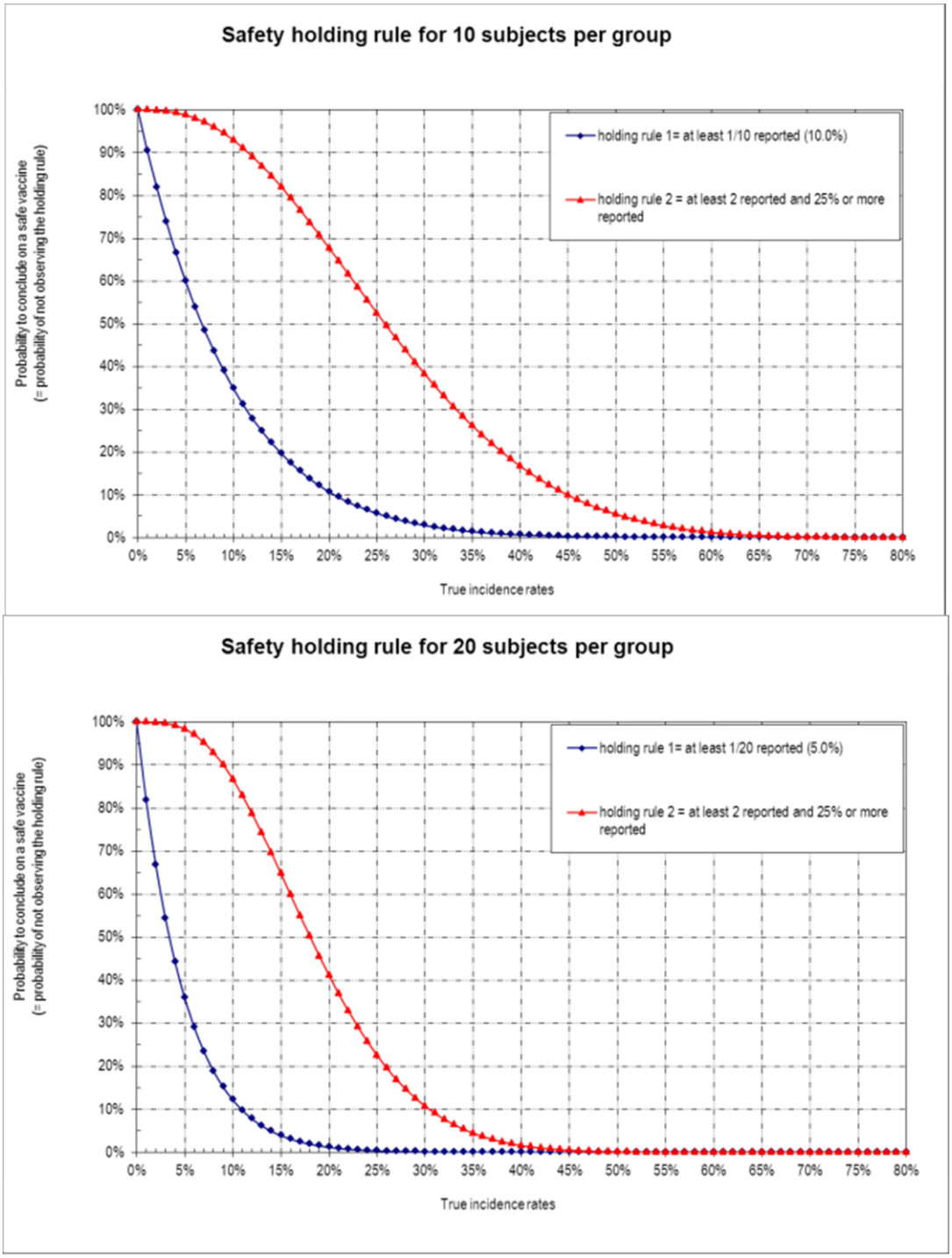
* Grading of biochemistry parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see APPENDIX C).

Risk assessment curves - probability of meeting holding rules

Figure 3 illustrates for example that:

- **With 10 subjects/ group:**
  - Each holding rule 1 (a-c) has more than 90% chance of not being met for a vaccine with a true incidence rate below 1% and has more than 90% chance of being met for a vaccine with a true incidence rate above 20%.
  - Each holding rule 2 (a-c) has almost 100% chance of not being met for a vaccine with a true incidence rate below 1% and has more than 30% chance of being met for a vaccine with a true incidence rate above 20%.
- **With 20 subjects/ group:**
  - Each holding rule 1 (a-c) has more than 80% chance of not being met for a vaccine with a true incidence rate below 1% and has more than 98% chance of being met for a vaccine with a true incidence rate above 20%.
  - Each holding rule 2 (a-c) has almost 100% chance of not being met for a vaccine with a true incidence rate below 1% and has more than 55% chance of being met for a vaccine with a true incidence rate above 20%.

Figure 3 **Risk assessment curves for safety holding rules 1 and 2 for treatment arms of 10 or 20 subjects (no adjustment for multiplicity)**



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. 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 to contact those subjects who do not return for scheduled visits or follow-up.

All data collected until the date of withdrawal/ last contact with the subject will be used for the analysis. If the subject agrees, the investigator should make an attempt to collect safety information until the initially planned date for study conclusion, either by phone, or by inviting the subject to a site visit around Day 450.

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:

- SAE.
- Non-serious AE.
- Protocol violation (specify).
- Consent withdrawal, not due to an AE*.
- 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 (S)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 (S)AE until resolution of the event (see Section 9.5.1.2).

10.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine 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 investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol (see also Section 7.5).

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

- SAE.
- Non-serious AE.
- Other (specify).

10.3. 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 endpoints

- Occurrence of each solicited local adverse event (AE), during the 7-day follow-up period *(i.e.* day 0 - 6) following each vaccination, in all subjects.
- Occurrence of each solicited general AE, during the 7-day follow-up period (*i.e.* day 0 - 6) following each vaccination, in all subjects.
- Occurrence of any unsolicited AE, during the 30-day follow-up period (*i.e.* day 0 - 29) following each vaccination, in all subjects.

- Occurrence of each haematological/ biochemical laboratory abnormality at Day 0, Day 7, Day 30, Day 60, Day 67, Day 90, Day 270 and Day 450, in all subjects.
- Occurrence of any potential immune-mediated disease (pIMD) from first vaccination up to study conclusion, in all subjects.
- Occurrence of any serious adverse event (SAE) from first vaccination up to study conclusion, in all subjects.

11.2. Secondary endpoints

- Anti-PD, anti-PE and anti-PilA total IgG antibody concentrations as measured by ELISA, at Day 0, Day 30, Day 60, Day 90, Day 270 and at Day 450, in all subjects.
- NTHi-specific cell-mediated immune responses as measured by flow cytometry intracellular cytokine staining (ICS) (frequency of specific $CD4^+/CD8^+$ T-cells expressing two or more markers, such as IL-2, IL-13, IL-17, IFN-γ, TNF-α and CD40L), at Day 0, Day 90, Day 270 and at Day 450, in a sub-cohort of subjects.

11.3. Tertiary endpoints (Amended 15 April 2016)

- Number of cases of NTHi-associated moderate and severe AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Number of cases of NTHi-associated AECOPD (any severity), over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Number of cases of moderate and severe AECOPD (any cause), over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Number of cases of AECOPD (any cause, any severity), over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Time to first AECOPD, in all subjects.
- Assessment of EXACT-PRO score, daily at bedtime throughout the study, in all subjects.
- NTHi presence in sputum, at Screening, Day 90, Day 180, Day 270, Day 360 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.
- Assessment of *CAT* score, at Screening, Day 270 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.
- Assessment of SGRQ-C score, at Screening, Day 270 and Day 450, in all subjects.
- Assessment of mMRC scale, at Screening, Day 270 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.
- Occurrence of rescue medication use, over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.
- Occurrence of healthcare use for AECOPD, over a period starting 1 month post-Dose 2 and lasting for 1 year, in all subjects.

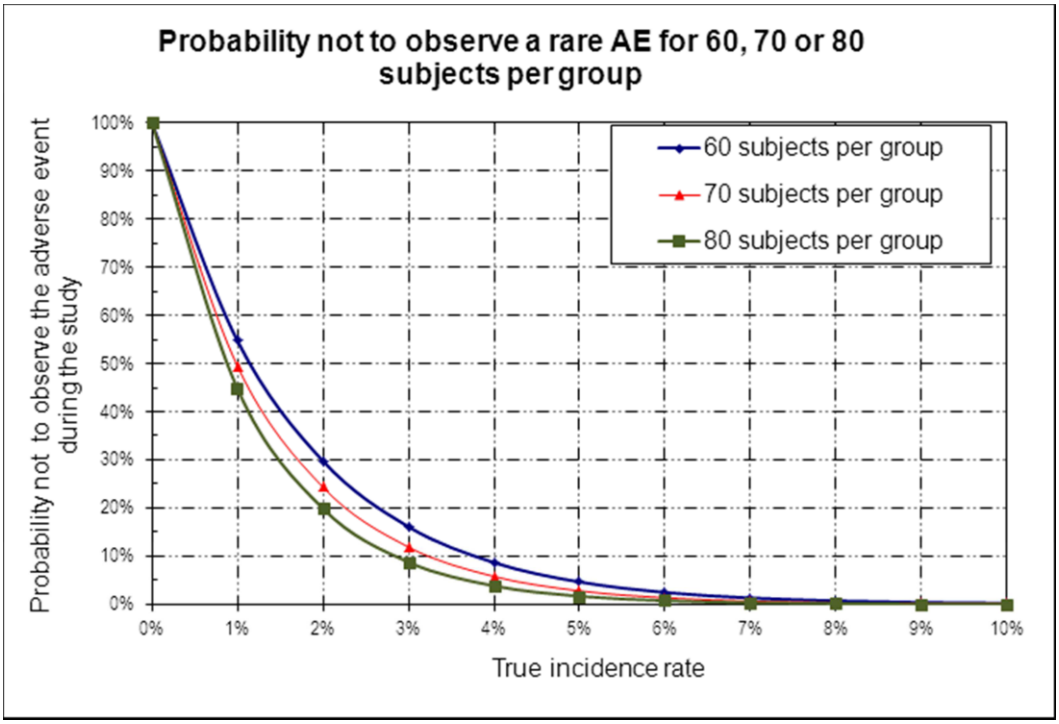
- Assessment of FEV1% of predicted normal value at Screening, Day 270 and Day 450, in all subjects.
- Assessment of 6MWT score, at Screening and Day 450, in all subjects.
- Occurrence of selected biomarkers in a subset of blood samples, at Day 0 and Day 450, and from first vaccination to study conclusion for each AECOPD, in all subjects.
- ***Presence of respiratory viral pathogens in sputum (including respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) at Screening, Day 90, Day 180, Day 270, Visit Day 360 and Day 450 and at each AECOPD visit from first vaccination to study conclusion, in all subjects.***

11.4. Determination of sample size

This study is a Phase II safety study to assess safety and reactogenicity of the investigational vaccine in moderate and severe COPD patients.

Considering the sample size of 70 in the group 10-AS01E, Figure 4 illustrates the probability of detecting an AE with true occurrence rate 0 - 10%.

Figure 4 Probability not to observe an AE for 60, 70 or 80 subjects per group



From Figure 4, it can be seen that with a sample size of 70 subjects per group, there is more than 50% of chance to detect an AE with a true incidence of 1%, and more than 97% of chance to detect an AE with a true incidence of 5%.

11.5. Study cohorts to be analysed

The following study cohorts will be evaluated.

11.5.1. Total vaccinated cohort

The Total vaccinated cohort (TVC) will include all subjects with at least 1 study vaccine administration documented:

- A **safety** analysis based on the TVC will include all vaccinated subjects.
- An **immunogenicity/ efficacy** analysis based on the TVC will include all vaccinated subjects for whom immunogenicity/ efficacy data are available.

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

11.5.2. ATP cohort for analysis of immunogenicity

The ATP cohort for immunogenicity will include all subjects in the TVC:

- Who met all eligibility criteria.
- For whom the administration route and site of the vaccines was according to protocol.
- Who complied with the vaccination schedule, as specified in Table 9.
- Who received the study vaccines according to protocol procedures.
- Who did not receive a concomitant medication/ product leading to elimination from the ATP analysis for immunogenicity (see Section 7.6.2), up to the 1 month post-Dose 2 visit (Day 90).
- Who did not present with an intercurrent medical condition leading to elimination from the ATP analysis for immunogenicity (see Section 7.7), up to the 1 month post-Dose 2 visit (Day 90).
- Who complied with the blood sample timings as specified in Table 9, at the 1 month post-Dose 2 visit (Day 90).
- For whom post-vaccination immunogenicity results are available for at least 1 assay.

11.5.3. ATP cohort for analysis of persistence of immunogenicity

The ATP cohort for persistence of immunogenicity will include all evaluable subjects, *i.e.*, those who were included in the ATP cohort for immunogenicity, or were excluded from this cohort solely because they had no blood samples taken or because of incompliance with blood sample timings up to the 1 month post-Dose 2 visit, and:

- Who did not receive a concomitant medication/ product leading to elimination from the ATP analysis for immunogenicity (see Section 7.6.2).
- Who did not present with an intercurrent medical condition leading to elimination from the ATP analysis for immunogenicity (see Section 7.7).

- Who complied with the blood sample timings after the 1 month post-last vaccination visit as specified in Table 9.
- For whom persistence immunogenicity results are available for at least 1 assay.

11.5.4. ATP cohort for analysis of efficacy

The ATP cohort for analysis of efficacy will include all subjects in the TVC:

- Who met all eligibility criteria.
- For whom the administration route and site of the vaccines was according to protocol.
- Who complied with the vaccination schedule, as specified in Table 9.
- Who received the study vaccine according to protocol procedures.
- Not having received a medication/ product/ vaccine that may lead to elimination from the ATP analysis for efficacy (see Section 7.6.3).

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.

Safety

- For solicited symptoms, the analysis will exclude subjects with missing or un-evaluable measurements (*i.e.* total analysis of solicited symptoms will include all vaccinated subjects with documented solicited symptom sheets).
- For the unsolicited symptoms and concomitant medications/ products/ vaccinations, subjects who miss reporting symptoms/concomitant medications/ products/ vaccinations will be treated as subjects without unsolicited symptoms or concomitant medications/ products/ vaccinations, respectively.

Immunogenicity

- For a given subject and the analysis of a given immunogenicity measurement, missing or un-evaluable measurements will not be replaced.
- A seronegative subject is defined as a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is defined as a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- 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.

- 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.

Impact of the investigational vaccine on AECOPD

- For a given subject and the analysis of a given laboratory assay, missing or un-evaluable measurements will not be replaced.
- Subjects who did not have any sputum collected during at least 1 AECOPD (if at least 1 AECOPD occurred) will not be taken into account for the NTHI-associated AECOPD analyses.
- For summaries of the number of AECOPD occurring during the 1 year follow-up period starting 1 month post-Dose 2, an exacerbation rate 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 for the rate of exacerbations during the 1 year follow-up period since the modelling of exacerbations takes into account the number of exacerbations and the time of follow-up for each subject. 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

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.

11.7. Analysis of demographics

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

- Frequency tables will be generated for categorical variable such as geographical ancestry;
- Mean, median and standard error 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.

11.8. Analysis of safety

The analysis will be performed on the TVC. If the percentage of vaccinated subjects excluded from the ATP cohort for efficacy is at least 10%, a second analysis will be performed on the ATP cohort for efficacy to complement the first analysis.

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 0 – day 6) or the 30-day (day 0 – day 29) 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 0 to day 6) 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.

For each group and for each **haematology/ biochemistry parameter:**

- The percentage of subjects having results below or above the local laboratory normal ranges will be tabulated by time point.
- The maximum grading from Screening up to study conclusion will be tabulated. Grades will be based on the FDA Guidance for Industry “Toxicity Grading Scale for

Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see APPENDIX C).

The number of subjects who experienced any **pIMD** or any **SAE** from first vaccination up to 6 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 exposures from first vaccination up to 6 months after last vaccination 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 0 – day 6) and during the 30-day follow-up period (day 0 – day 29) will be summarised per group for each dose and overall per dose.

11.8.1. iSRC safety evaluations

Unblinded review of safety data will be done during iSRC evaluations (refer to Section 9.10 for more information). No individual clinical study report will be written as a result of these safety evaluations.

11.9. Analysis of immunogenicity

The analysis will be performed on the ATP cohort for immunogenicity. 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.

Humoral immune response

Within group evaluation

For each group, at each time point during which blood samples are collected for humoral immune response and for each assay:

- Seropositivity rate and their exact 95% CI will be tabulated.
- GMCs and their 95% CI will be calculated.

For each group, at each time point during which blood samples are collected for humoral immune response:

- Antibody concentrations distribution will be investigated using Reverse Cumulative Curves.

Between groups evaluation

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 a***n*** ANCOVA model ***that considers heterogeneity of variances (via Proc Mixed) on the logarithm10 transformation of the concentrations***. Th***is model*** will include ***country,*** the group, age category (40 - 59 years or 60 - 80 years), number of moderate and severe AECOPD in the year before vaccine Dose 1 (< 2 or ≥ 2), GOLD grade (GOLD 2 or GOLD 3) ***and pre-Dose 1 concentration (as covariate)*** as fixed effects. **(Amended 15 April 2016)**

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

Cell-mediated immune response

The frequency of specific $CD4^+$/ $CD8^+$ T-cells will be summarised by group, at each time point during which blood samples are collected for CMI (descriptive statistics).

11.10. Analysis of impact of the investigational vaccine on AECOPD

The analysis will be performed on the ATP cohort for efficacy. If the percentage of vaccinated subjects excluded from the ATP cohort for efficacy is more than 10%, a second analysis based on the TVC will be performed to complement the first analysis.

The following incidence rates will be computed over a period starting 1 month post-Dose 2 and lasting for 1 year, with 95%CI:

- NTHi-associated moderate and severe AECOPD.
- NTHi-associated all-severity AECOPD.
- All-cause moderate and severe AECOPD.
- All-cause, all-severity AECOPD.

The 95% CI of the incidence rate will be computed using a model which accounts for repeated events. The Generalised linear model assuming the Negative Binomial distribution for the response variable with logarithm as link function, and the logarithm of time for follow-up as an offset variable will be used. If the model does not converge, the Poisson distribution will be used instead of the Negative Binomial one.

Vaccine efficacy (VE) for AECOPD events will be defined as:

$$VE\ (AECOPD) = 1 - R_{vaccine} / R_{control}$$

with:

- $R_{vaccine}$ = average yearly incidence rate of AECOPD events per subject in the group 10-AS01E.
- $R_{control}$ = average yearly incidence rate of AECOPD events per subject in the Control group.

In case the 95% CI of the VE cannot be estimated, *e.g.* when no event is observed in the group 10-AS01E (leading to a VE of 100%), then an exact procedure will be used to estimate a VE and its 95% CI. This exact procedure will be based on the number of subjects with event instead of on the average number of event per subject in each group.

VE in the prevention of NTHi-associated moderate and severe AECOPD and its 95% CI will be calculated.

VE in the prevention of NTHi-associated all-severity AECOPD, of all-cause moderate and severe AECOPD and of all-cause, all-severity AECOPD and their 95% CI will also be calculated.

The time until first AECOPD as of 1 month post-Dose 2 will be computed with exact 95% CI by group. Subjects who exacerbate before 1 month post-Dose 2 will not be taken into account in this analysis.

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 95% CI will be estimated assuming independence of bacterial results across sputum samples.

11.11. Analysis of HRQOL, lung capacity and exercise capacity

The analysis will be performed on the TVC. If the percentage of vaccinated subjects excluded from the ATP cohort for efficacy is at least 10%, a second analysis will be performed on the ATP cohort for efficacy to complement the first analysis.

Descriptive statistics (median, mean, range, standard deviation, first and third quartiles) on the **EXACT-PRO,** ***CAT***, **SGRQ-C** and **mMRC** scores, on **FEV_1% of predicted normal value** and on the **6MWT** scores will be tabulated by specified visit.

Descriptive summaries **rescue medication and healthcare use for AECOPD** will be provided.

11.12. Analysis of selected biomarkers

The analysis will be performed on the ATP cohort for efficacy. If the percentage of vaccinated subjects excluded from the ATP cohort for efficacy is at least 10%, a second analysis will be performed on the TVC to complement the first analysis.

For each type of timepoint during which blood samples are collected for analysis of biomarkers, descriptive statistics (median, mean, range, standard deviation, first and third quartiles) will be tabulated for each selected biomarker.

11.13. Interpretation of analyses

Comparative analyses with the aim to characterise the difference in reactogenicity/ immunogenicity/ efficacy between groups will be descriptive. These descriptive analyses should be interpreted with caution.

11.14. 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.

11.14.1. Sequence of analyses (Amended 15 April 2016)

The analyses will be performed stepwise:

- The analysis of data up to Visit 6 (Day 90) will be performed in a first step. This analysis will include:
  - The final analysis of immunogenicity and solicited AEs post-Dose 1 and post-Dose 2.
  - The assessment of unsolicited AEs, SAEs and pIMDs up to 30 days post-Dose 1 and post-Dose 2 on as cleaned as possible data.

  This analysis will be documented in a statistical report. At this point, the GSK statistician of the project (or delegates) will be unblinded (*i.e.* will have access to the individual subject treatment assignments).
- ***The analyses of the impact of the investigational vaccine on AECOPD will be performed in parallel with the first step. This will include:***
  - the analyses of fresh sputum samples (culture) obtained up to ***the data lock point of the interim analysis***.
  - ***The analyses of AECOPD obtained up to the data lock point of the interim analysis.***
- The final analysis of data up to study conclusion will be performed in a second step, once those data will be available and cleaned. This analysis will include:
  - The final analysis of immunogenicity at Day 270 and Day 450.
  - SAEs and pIMDs up to Day 450 on cleaned data.
  - Impact of the investigational vaccine on AECOPD, HRQOL, lung function, exercise capacity and biomarkers.

  In addition, all previous analyses will be re-produced based on cleaned data at this point.

Individual listings will only be provided at this stage. ***An integrated*** study report containing data from the entire study will be written ***at the end of the study*** and will be made available to the investigators.

11.14.2. Statistical considerations for interim analyses

All analyses are descriptive, and performed on final or as clean as possible data therefore no adjustment needs to be performed.

12. ADMINISTRATIVE MATTERS

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

12.1. Case Report Form/Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, 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 of omissions or inconsistencies with documentation and approval 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 others, 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 RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE 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. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will freeze completed and approved screens at each visit.

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. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. 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 15 years.

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

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

Summaries of the results of GSK interventional studies (Phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit.

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.

13. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

14. REFERENCES

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APPENDIX A LABORATORY ASSAYS

Humoral antibody responses (Amended 15 April 2016)

Anti-PD antibodies

Anti-PD antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PD antibodies will be determined, using in-house made reference serum. The current cut-off of the assay is ***153*** EL.U/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 cut-off of the assay is 8 EL.U/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 cut-off of the assay is 7 EL.U/mL.

Cell-mediated immunity

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.

Microbiological assessments

Bacterial pathogen identification and bacterial load

Evidence and identification of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and other bacterial pathogens (including *S. aureus*, *P. aeruginosa* and *S. pyogenes*) in sputum specimens will be investigated using standard microbiological culture and standard bacteriological procedures [Murray, 1999] according to local laboratory procedures. In addition, semi-quantitative data using the culture quadrant assessment method will be collected for these pathogens.

H. influenzae, *S. pneumoniae* and *M. catarrhalis* will be detected and quantified by mean of a qualified GSK proprietary triplex real-time PCR assay *P. aeruginosa, S. aureus* and *S. pyogenes* will be detected by means of a qualified GSK proprietary triplex real-time PCR assay.

Viral pathogen identification and viral load

Respiratory viral pathogens will be diagnosed by mean of a commercial and qualified multiplex PCR assay (RVP Fast, Luminex).

Rhinovirus-specific quantitative PCRs will be ***performed on a subset of sputum samples*** at GSK Biologicals or at a designated GSK Biological laboratory. **(Amended 15 April 2016)**

APPENDIX B CLINICAL LABORATORIES

Table 25 GSK Biologicals' laboratories (Amended 15 April 2016)

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 26 Outsourced laboratories (Amended 15 April 2016)

Laboratory	Address
BARC NV	Industriepark Zwijnaarde 3b B-9052 Gent Belgium
BUGS Bioscience Ltd, London Bioscience Innovation Centre	***2 Royal College Street, NW1 0NH Greater London, United Kingdom***

APPENDIX C FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007)

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

i. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (*e.g.*, a certain number of AEs, as defined in the table, may call for stopping the study). Less extreme observations (*e.g.*, mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements

are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.

ii. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

iii. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, and 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categories adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

a. Tables for Clinical Abnormalities

Note from the sponsor: The tables in this section of the guidance will not be used in this particular study. Instead, the parameters as provided in the NTHI-004 study protocol are to be used.

b. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Table 27 FDA toxicity grading scales for hematology/ biochemistry parameters

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia **Fasting – mg/dL** **Random – mg/dL**	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	D3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
*** "ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm^3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm^3	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1 500	1 501 - 5 000	> 5 000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	D1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intra vascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

iv. REFERENCES for the Appendix A

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)
2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)
3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)
4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)
5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)
6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.

APPENDIX D AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	200157 (NTHI-004)
EudraCT number	2013-003062-13
Amendment number:	Amendment 1
Amendment date:	27 March 2014
Co-ordinating author:	PPD (XPE Pharma & Science for GSK Biologicals)

Rationale/background for changes:

Protocol amendment 1 was prepared:

- Because the volumes of the individual blood samples that will be collected were re-distributed after discussion with the central laboratory. The total volume of blood collected per subject across scheduled visits and at AECOPD visits remains similar.
- Because information on processing and storage temperature until shipment was updated for some of the samples after discussion with the central laboratory.
- To clarify that the plasma obtained during PBMC processing will be kept for potential future additional testing.
- To clarify that white blood cell differential count will be done on blood samples for safety assessment.

In addition, some other, minor clarifications have been made and the list of contributing authors has been updated.

Added text is presented in ***bold italics*** and deleted text in ~~strikethrough~~ in the following sections:

Title page

Contributing authors

- PPD ***and*** PPD ***(Business & Decision for GSK Biologicals)***, GVCL Study Manager***s***

List of abbreviations

PBMC	Peripher~~i~~eal blood mononuclear cell

Section 6.5.1. List of study procedures during scheduled study visits

Table 7 List of study procedures during scheduled study visits

Epoch
Type of contact
Timepoint
Sampling timepoint
Blood sampling:
For safety assessment (***~5.5*** ~~5~~ mL)
For humoral immunogenicity (***~25.5*** ~~27~~ mL)
For CMI (~40 mL) [e]
For biomarkers (***~12.8*** ~~12~~ mL)

Section 6.5.2. List of study procedures during AECOPD-driven study visits and phone contacts

Table 8 List of study procedures during AECOPD-driven study visits and phone contacts

Type of contact
Timepoint
Sampling timepoint
Blood sampling:
For biomarkers (***~12.8*** ~~12~~ mL)

Section 6.6.15. 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.

Section 6.6.15.1. Blood Samples

Blood samples for safety assessment

A volume of approximately ***5.5*** ~~5~~ mL of whole blood should be drawn from all subjects at each pre-defined timepoint ***and will be split and processed as follows:***

- ***Approximately 2 mL of whole blood will be collected for haematology assessment. These samples will not be processed They should be kept at room temperature and shipped on the day of collection.***
- ***Approximately 3.5 mL of whole blood will be collected for biochemistry assessment and will be processed to serum. After processing, serum samples should be kept at room temperature and shipped on the day of collection.***

(An) additional blood sample(s) for safety assessment may need to be drawn before administration of vaccine Dose 2, or during other study visits if deemed necessary by the investigator (see Table 10). ~~These samples will not be processed. They should be kept at room temperature and shipped on the day of collection.~~

Blood samples for humoral immunogenicity

A volume of approximately ***25.5*** ~~27~~ mL of whole blood should be drawn from all subjects at each pre-defined timepoint ~~(to provide at least 9 mL and ideally ~13 mL of serum)~~. After processing, serum samples should be kept at -20°C until shipment.

Blood samples for biomarkers

A volume of approximately ***12.8*** ~~12~~ mL of whole blood should be drawn from all subjects at each predefined timepoint and will be split and processed as follows:

- Approximately 5 mL of whole blood will be ***processed to serum*** ~~used to provide at least 1.5 mL and ideally 2.5 mL of serum~~. After processing:
  - ***An aliquot of serum should be kept at room temperature and shipped on the day of collection.***
  - ***The remaining*** serum ~~samples~~ should be kept at ***-70/80*** ~~-20~~°C until shipment.
- Approximately ***6*** ~~5~~mL of whole blood will be ***processed to plasma*** ~~used to provide at least 1.5 mL and ideally 2.5 mL of plasma~~. After processing, plasma samples should be kept at -70/80°C until shipment.
- Approximately 1.8 mL of whole blood will ***be processed to plasma*** ~~not be processed~~. ***After processing, plasma*** ~~These~~ samples should be ***kept at -70/80°C until shipment*** ~~kept at room temperature and shipped on the day of collection~~.

Section 6.6.15.2. Sputum samples

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

Section 6.7.2. Biological samples

Table 10 Biological samples

Sample type	Quantity	Unit
Blood for safety assessment	~***5.5*** ~~5~~	mL
Blood for humoral immunogenicity	~***25.5*** ~~27~~	mL
Blood for CMI	~40	mL
Blood for biomarkers	~***12.8*** ~~12~~	mL

Section 6.7.3 Laboratory assays

Haematology/ biochemistry

Table 11 Haematology and biochemistry

System	Discipline	Component	Method	Scale	Laboratory*
Whole blood	Haematology	Haemoglobin	commercial	Quantitative	Central laboratory
		Platelets	commercial	Quantitative	
		White Blood Cells (WBC) **	commercial	Quantitative	

*Refer to APPENDIX B for the laboratory address.

*** Including WBC differential count.***

Humoral antibody responses

Table 12 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory*
Serum	Anti-PD	ELISA	In house	EL.U/mL	100 ***	GSK Biologicals**

EL.U/mL = ELISA unit per millilitre
*Refer to APPENDIX B for the laboratory addresses.
** GSK Biologicals laboratory refers to the Global Vaccines Clinical Laboratories (GVCL) in Rixensart, Belgium; Wavre, Belgium; Laval, Canada.
*** ***A new cut-off may be defined after re-validation of the anti-PD ELISA.***

Serum ***and plasma*** samples might also be used for **development and/ or evaluation of other assays** to measure the immune response to the investigational NTHi vaccine ***components and/or to other NTHi antigens*** such as, but not limited to, ~~serum~~ bactericidal activity assay, assays measuring functional antibodies, immunochemistry assays for other immunoglobulin classes and/or for anti-IgG subclasses.

Additional testing on serum ***and plasma*** samples 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.

Cell-mediated immune responses

Additional testing on Peripher~~ic~~al Blood Mononuclear Cells (PBMCs), such as, but not limited to, evaluation of NTHi-specific memory B-cells, 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 obtained during the processing of whole blood to obtain PBMCs will be stored for potential future analyses and/ or assay development purposes.

Appendix A Laboratory assays

Humoral antibody responses

Anti-PD antibodies

Anti-PD antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PD antibodies will be determined, using in-house made reference serum. The ***current*** cut-off of the assay is 100 EL.U/mL. ***This assay will however be re-validated according to the latest validation standards and a new cut-off might be defined based on a precise and accurate limit of quantification.***

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 2

eTrack study number and Abbreviated Title	200157 (NTHI-004)
EudraCT number	2013-003062-13
Amendment number:	Amendment 2
Amendment date:	15 December 2014
Co-ordinating author:	PPD (XPE Pharma & Science for GSK Biologicals)

Rationale/background for changes:

Protocol amendment 2 was prepared:

- To add clarification in the tertiary objectives: because acute exacerbations of COPD are complex events, triggered by multiple (interacting) pathogens, assessing the natural immunity to other pathogens might be important for interpretation of the data.
- To add an additional blood sample for haematology assessment at each AECOPD visit. This blood sample will be collected to describe the systemic inflammation at time of exacerbation in terms of white blood cells and differential cell counts.
- To clarify the list of concomitant medication that may lead to elimination of a subject from ATP analysis of immunogenicity (Section 7.6.2): because oral corticosteroids are commonly used in treatment of exacerbations, the administration of oral corticosteroids given for this indication will not fall under the definition of "chronic administration of immunosuppressants or other immune-modifying drugs at any time during the study period", used to determine elimination from the ATP analysis of immunogenicity.
- To add a benefit: risk assessment section (Section 1.3).

In addition, a typo in the footnote of the table of intervals between visits (Table 9) has been corrected and the list of contributing authors has been updated.

Added text is presented in ***bold italics*** and deleted text in ~~strikethrough~~ in the following sections:

Title page

Contributing authors

- PPD (PPD ***Novellas Healthcare*** for GSK Biologicals), Study Delivery Manager

- PPD ~~and~~ PPD, PPD *and* PPD, Safety Representatives
- PPD (Aixial Pharma for GSK Biologicals) *and* PPD, Study Data Manager

Section 1.3 Benefit: Risk assessment

Please refer to the current IB for the summary of potential risks and benefits of the NTHi investigational vaccine.

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

1.3.1 Risk Assessment

Important Potential/Identified Risk	*Data/Rationale for Risk*	*Mitigation Strategy*
	NTHi 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 (data from two studies using NTHi vaccines: NTHI-002 (non-adjuvanted formulations) and NTHI-003 (adjuvanted and non-adjuvanted formulations).*	*Close monitoring of potential immune-mediated diseases in clinical development programs using adjuvants systems. The potential risk of events of possible autoimmune aetiology to occur is mentioned in the Informed Consent Form (ICF).*

1.3.2 Benefit Assessment

Benefits considerations include:

- ***Contribution to the process of developing of a vaccine against AECOPD.***
- ***Medical evaluations/assessments associated with this study (i.e. physical examination, blood testing [haematology and biochemistry data], spirometry).***

1.3.3 Overall Benefit : Risk Conclusion

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

Synopsis: Tertiary objectives + Section 2.3 Tertiary objectives

- To collect blood and sputum samples for assay development, for disease diagnostic purpose, for lung microbiome analysis and/ or for additional evaluation of the immune responses to the investigational vaccine ***and to other potential pathogens involved in AECOPD.***

Synopsis: Sampling schedule

– ***Blood samples for assessment of haematology parameters will be collected at each AECOPD visit.***

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

GSK Biologicals will prepare a model ~~Informed Consent Form (~~ICF~~)~~ which will embody the ICH GCP and GSK Biologicals required elements.

Section 6.5.2. List of study procedures during AECOPD-driven study visits and phone contacts

Table 8 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] and/ or visit[s])
Timepoint	within 96 hours of onset symptoms	at least every 2 weeks as of AECOPD visit until AECOPD has resolved [(a)]
Sampling timepoint	AECOPD	
Blood sampling:		
For biomarkers ***(~***12.8 mL)	•	
For haematology assessment (~2.0 mL)	•	

Section 6.5.4. Interval between study visits

Table 9 Interval between study visits

Footnote:

[5] Scheduled study visits should not take place within 7 days of an AECOPD visit. If an AECOPD occurs at the time of a scheduled study visit so that this is not adhered to, the scheduled visit should be re-scheduled to a later date within the time window specified. In consultation with GSK, only ~~Visit 8 (Day 270) and~~ Visit 10 (Day 450) may exceptionally be conducted outside of the allowed interval if necessary.

Section 6.6.15 Blood samples

Blood samples for safety assessment

For scheduled visits: a ~~A~~ volume of approximately 5.5 mL of whole blood should be drawn from all subjects at each pre-defined timepoint ***(Table 10)*** and will be split and processed as follows:

Blood samples for biomarkers

At Visit 1, Visit 10 and at each AECOPD visit: ~~A~~ a volume of approximately 12.8 mL of whole blood should be drawn from all subjects ~~at each pre-defined timepoint~~ and will be split and processed as follows:

- Approximately 5 mL of whole blood will be processed to serum. After processing:
  - An aliquot of serum should be kept at room temperature and shipped on the day of collection.
  - The remaining serum should be kept at -70/80°C until shipment.
- Approximately 6 mL of whole blood will be processed to plasma. After processing, plasma samples should be kept at -70/80°C until shipment.
- Approximately 1.8 mL of whole blood will be processed to plasma. After processing, plasma samples should be kept at -70/80°C until shipment.

At each AECOPD visit: a volume of approximately 2 mL of whole blood will be collected for haematology parameters from all subjects (Table 10). These samples will not be processed. They should be kept at room temperature and shipped on the day of collection.

Section 6.7.2. Biological samples

Table 10 Biological samples

Blood for safety assessment * ***(haematology and biochemistry)***	~5.5	mL	• Screening Visit (pre-Day 0)	All screened subjects
			• Visit 1 (Day 0) • Visit 2 (Day 7) • Visit 3 (Day 30) • Visit 4 (Day 60) • Visit 5 (Day 67) • Visit 6 (Day 90) • Visit 8 (Day 270) • Visit 10 (Day 450)	All enrolled subjects
Blood for haematology parameters	***~2.0***	***mL***	• ***During each AECOPD***	***All enrolled subjects***

Section 6.7.3. Laboratory assays

Haematology/ biochemistry

Haematology/ biochemistry assays for safety assessment will be performed in a central laboratory. ***Haematology assays on whole blood taken at AECOPD visits will be performed in the same central laboratory.***

Section 7.6.2. Concomitant medications/products and vaccines that may lead to the elimination of a subject from ATP analysis for immunogenicity

- Immunosuppressants or other immune-modifying drugs administered chronically (*i.e.* more than 14 days) at any time during the study period (*e.g.* methotrexate). ~~For corticosteroids, this will mean prednisone ≥ 10 mg/day, or equivalent. Topical steroids are allowed.~~ ***Use of corticosteroids is allowed as per local treatment recommendations.***

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 3

eTrack study number and Abbreviated Title	200157 (NTHI-004)
EudraCT number	2013-003062-13
Amendment number:	Amendment 3
Amendment date:	15 April 2016
Co-ordinating author:	PPD (XPE Pharma & Science for GSK Biologicals)

Rationale/background for changes:

- In compliance with ICH requirements, the protocol mentions that all results will be presented in an integrated report at the end of the study.
- Following re-development and re-validation of the anti-PD ELISA, a new cut-off was defined.
- Reference to the GSK Biologicals' Laval laboratory was removed, as this laboratory will not be used in the study. In addition, this laboratory is no longer part of GSK Biologicals' laboratories.
- Internal assay qualification procedures were revised and it was decided that the level of characterisation of the ELISA assays can be minimal (set-up level) for this study as immunogenicity data are descriptive. In consequence, the assays will be standardized but not qualified as stated in the original version.This change will not impact the validity of the results.
- A tertiary endpoint was added as the presence of viral pathogens in sputum will be examined as part of microbiome analysis.
- In order to see early effects of the vaccine on the microbiome, analysis on fresh sputum samples (culture results) will be done on all available data up to the data lock point of the interim analysis.
- In order to have a first look whether or not the investigational vaccine has an impact on AECOPD, AECOPD analyses will be done up to the data lock point of the interim analysis.
- Wording was added to clarify process for collection of sputum *H. influenzae* sweeps.
- Wording was updated in order to be aligned with the Statistical Ananlysis Plan.
- In addition, minor edits in other sections were made for clarification purposes.

Added text is presented in ***bold italics*** and deleted text in ~~strikethrough~~ in the following sections:

Title page

Co-ordinating and contributing authors

Co-ordinating author

PPD, PPD (XPE Pharma & Science for GSK Biologicals)

Contributing authors

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- PPD and PPD ~~(Business & Decision for GSK Biologicals)~~, ***CLS***~~GVCL~~ ***Laboratory*** Study Managers
- PPD, PPD, PPD PPD and PPD, PPD Safety Representatives
- PPD (Aixial Pharma for GSK Biologicals) and PPD, Study Data Manager
- PPD**,** ***Project Data Manager***
- PPD, PPD**,** Global Regulatory Lead

Protocol Amendment 3 Sponsor Signatory Approval page

Sponsor signatory ~~Jeanne-Marie Devaster, Director Clinical Research and Translational Science~~ ***Ashwani Kumar Arora*, *Clinical and Epidemiology Project Lead***

Synopsis and Section 11.3 Tertiary endpoints

Presence of respiratory viral pathogens in sputum (including respiratory syncytial virus, parainfluenza virus, enterovirus/ rhinovirus, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) at Screening, Day 90, Day 180, Day 270, Visit Day 360 and Day 450 and at each AECOPD visit from first vaccination to study conclusion, in all subjects.

List of abbreviations

CLS	***Clinical Laboratory Sciences***

Section 6.7.1 Use of specific study materials

When materials are provided by GSK Biologicals ***or by the central laboratory***, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner.

Section 6.7.3 Laboratory assays

Humoral antibody responses

Total IgG concentrations will be measured by ELISA at GSK Biologicals' laboratory. Standardised ~~and qualified~~ procedures will be used for all assays.

Table 12 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory*
Serum	Anti-PD	ELISA	In house	EL.U/mL	***153*** ~~100 ***~~	GSK Biologicals**
Serum	Anti-PE	ELISA	In house	EL.U/mL	8	GSK Biologicals**
Serum	Anti-PilA	ELISA	In house	EL.U/mL	7	GSK Biologicals**

EL.U/mL = ELISA unit per millilitre
*Refer to APPENDIX B for the laboratory addresses.
** GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences (CLS) Laboratories*** ~~Global Vaccines Clinical Laboratories (GVCL)~~ in Rixensart, Belgium; Wavre, Belgium~~; Laval, Canada.~~
~~*** A new cut-off may be defined after re-validation of the anti-PD ELISA.~~

Table 13 Cell-Mediated Immunity

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**

PBMC = Peripheral Blood Mononuclear Cell; ICS = Intracellular Cytokine Staining
*Refer to APPENDIX B for the laboratory addresses.
** GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences (CLS)*** ~~Global Vaccines Clinical Laboratories (GVCL)~~ in Rixensart, Belgium; Wavre, Belgium~~; Laval, Canada~~.

Further **characterisation of bacterial serotypes and/ or genotypes** on ~~stored *H. influenzae* positive sputum and/ or o~~n stored ***H. influenzae*** sweeps ~~of positive *H. influenzae* culture plates may~~ ***will*** be done at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using either standard agglutination techniques or molecular tools***, as microarray serotyping; considering that a "stored H. influenzae sweeps" is defined as the "harvest" of all microorganisms that have grown on the primary sputum culture plate (e.g. chocolate agar plate for H. influenzae growth) if at least one H. influenzae colony was observed on this plate.***

Bacterial pathogen identification (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 stored sputum samples will be performed at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals using molecular methods such as multiplex ***RT*** PCR and/ or quantitative PCR (qPCR).

In addition, viral pathogens (such as rhinovirus) in stored sputum samples ~~might~~ ***will*** be quantified ***on a subset of samples*** using qPCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using qualified procedures.

Table 14 Microbiology

System	Component	Method	Scale	Laboratory*
Bacterial pathogen identification				
			semi-quantitative	
Stored *H. influenzae* positive sputum and/ or stored sweep of positive *H. influenzae* culture plate	Characterisation of bacterial serotypes and/ or genotypes	Agglutination and/ or molecular tools ***(microarray serotyping)***	qualitative	GSK Biologicals** or designated laboratory

*Refer to APPENDIX B for the laboratory addresses.

** GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences (CLS) Laboratories*** ~~Global Vaccines Clinical Laboratories (GVCL)~~ in Rixensart, Belgium; Wavre, Belgium~~; Laval, Canada~~.

† Bacterial culture of sputum stored in STGG (alternative storage) might be performed in a subset of samples at specific sites and/ or at GSK Biologicals' designated laboratory. More details will be provided in the SPM and associated documents.

Section 11.9 Analysis of immunogenicity

Between groups evaluation

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 a***n*** ~~one-way~~ ANCOVA model ***that considers heterogeneity of variances (via Proc Mixed) on the logarithm10 transformation of the concentrations*** ~~on the logarithm10 transformation of the concentrations~~. Th***is model*** ~~e ANCOVA model~~ will include ***country,*** the group, age category (40 - 59 years or 60 - 80 years), number of moderate and severe AECOPD in the year before vaccine Dose 1 (< 2 or ≥ 2), ~~and~~ GOLD grade (GOLD 2 or GOLD 3) ***and pre-Dose 1 concentration (as covariate)*** as fixed effects ~~and the pre-Dose 1 concentration as regressor~~. ~~The groups will be considered significantly different if the 95% CI for the GMC ratio between the 2 groups does not contain the value 1~~.

Section 11.14.1 Sequence of analysis

- ***The analyses of the impact of the investigational vaccine on AECOPD will be performed in parallel with the first step. This will include:***
  - the analyses of fresh sputum samples (culture) obtained up to ***the data lock point of the interim analysis***.
  - ***The analyses of AECOPD obtained up to the data lock point of the interim analysis.***

  Individual listings will only be provided at this stage. ***An integrated*** ~~final~~ study report containing data from the entire study will be written ***at the end of the study*** and will be made available to the investigators.

Appendix A Laboratory assays

Humoral antibody responses

Anti-PD antibodies

Anti-PD antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PD antibodies will be determined, using in-house made reference serum. The current cut-off of the assay is ***153*** ~~100~~ EL.U/mL. ~~This assay will however be re-validated according to the latest validation standards and a new cut-off might be defined based on a precise and accurate limit of quantification.~~

Viral pathogen identification and viral load

Respiratory viral pathogens will be diagnosed by mean of a commercial and qualified multiplex PCR assay (RVP Fast, Luminex).

Rhinovirus~~- and respiratory syncytial virus-~~specific ~~real-time~~ quantitative PCR~~s~~ will be ~~developed and qualified~~ ***performed on a subset of sputum samples*** at GSK Biologicals or at a designated GSK Biological laboratory.

Appendix C Clinical laboratories

Table 25 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
~~GSK Biologicals Global Vaccine Clinical Laboratory, North America Laval~~	~~Biospecimen Reception - Clinical Serology 525 Cartier blvd West Laval Quebec Canada H7V 3S8~~
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 26 Outsourced laboratories

Laboratory	Address
BARC NV	Industriepark Zwijnaarde 3b B-9052 Gent Belgium
BUGS Bioscience Ltd, London Bioscience Innovation Centre	***2 Royal College Street, NW1 0NH Greater London, United Kingdom***

Protocol Amendment 3 Sponsor ignatory Approval

eTrack study number and Abbreviated Title	200157 (NTHI-004)
EudraCT number	2013-003062-13
Date of protocol amendment	Amendment 3 Final: 5 April 2016
Detailed Title	A Phase II, randomis d, observer-blind, placebo-controlled, multi-cen e study to evaluate the safety, reactogenicity and· unogenicity of GSK Biologicals' investig tional vaccine GSK2838504A, when administered *i* amuscularly according to a 0, 2 month schedule to C PD patients aged 40 to 80 years
Sponsor signatory (Amended 15 April 2016)	***Ashwani Kumar Arora, Clinical and Epidemiology Project Lead***
Signature	PPD [redacted]
Date	April 21 2016

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