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207759 (NTHI MCAT-008)
Protocol Amendment 3 Final

Clinical Study Protocol

Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'institut 89,1330 Rixensart, Belgium

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) multi-antigen vaccine consisting of three conserved surface proteins (PD, PE and PilA) from *Haemophilus influenzae* and one conserved surface protein (UspA2) from Mcat (GSK3277511A).
Other Study vaccine	Placebo
eTrack study number and Abbreviated Title	207759 (NTHI MCAT-008)
Investigational New Drug (IND) number	16531
EudraCT number	2017-002941-31
Date of protocol	Final Version 1: 28 July 2017
Date of protocol amendment:	Amendment 1 Final: 24 July 2018 Amendment 2 Final: 24 July 2019 Amendment 3 Final: 26 May 2020
Title	An observer-blind study to evaluate the safety, reactogenicity and immunogenicity of the investigational GSK Biologicals' COPD vaccine (GSK3277511A) in adults.
Detailed Title	A Phase 2, randomised, observer-blind, multi-centre study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' GSK3277511A investigational vaccine when administered intramuscularly according to two different vaccine schedules in adults aged 40 to 80 years old.
Co-ordinating author	PPD (XPE Pharma & Science for GSK Biologicals)

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Contributing authors **(Amended 26 May 2020)**	• PPD (Clinical & Epidemiology Project Lead) • PPD (Senior Clinical Research & Development Lead) and PPD (Clinical Research & Development Lead) • PPD (Study Statisticians) • PPD (Lead Statisticians) • PPD (Science Writers) • PPD (Study Delivery Leads) • PPD (Aixial for GSK Biologicals) (Clinical Trials Supply Manager) • PPD (CLS Clinical Read-out Team Leader) • PPD (CLS Study Managers)

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Contributing authors **(Amended 26 May 2020)**	• PPD (Clinical Safety Representatives) • PPD (Oversight Data Manager) • PPD (TCS for GSK Biologicals) and PPD (ICON for GSK Biological) (Study Data Managers) • PPD (Regulatory Affairs Representatives) • PPD (Global patents) • PPD (Vaccine Development Lead)

GSK Biologicals' Protocol DS v15.0

Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207759 (NTHI MCAT-008)
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Sponsor signatory	Ashwani Kumar Arora Clinical & Epidemiology Project Lead
Signature	_____
Date	_____

Protocol Amendment 3 Rationale

Amendment number:	Amendment 3

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the conduct or management of the trial.

Rationale/background for changes:

- This protocol amendment 3 outlines measures that may be applicable during special circumstances (e.g. COVID-19 pandemic). The purpose of the amendment is to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity.

However, if the study specific visit and procedures can be completed, then they should be completed according to the protocol, taking into account clinical judgment and local public health guidance to protect the safety of staff and subjects.

Amended text is indicated in ***bold italics*** in the body of the protocol. Detailed description of the changes is provided in APPENDIX C.

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' study 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 onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, 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.

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Date of protocol amendment	Amendment 3 Final: 26 May 2020
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Investigator name	_____
Signature	_____
Date	_____
PPD **name, function and title**	_____
Signature	_____
Date	_____

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 8.4.2.

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

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.8.

SYNOPSIS

(Amended 26 May 2020)

Detailed Title	A Phase 2, randomised, observer-blind, multi-centre study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' GSK3277511A investigational vaccine when administered intramuscularly according to two different vaccine schedules in adults aged 40 to 80 years old.
Indication	Active immunisation for the reduction of frequency of moderate and severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) in patients with a previous history of moderate or severe AECOPD.
Rationale for the study and study design	• Rationale for the study The purpose of this Phase 2 study is to evaluate two vaccine schedules of the investigational NTHi-Mcat vaccine. As the prevalence of COPD increases with age and as age has an influence on both the immunogenicity and reactogenicity of a vaccine, subjects 40–80 years old will be enrolled. As cigarette smoking is the most commonly encountered risk factor for COPD, adults with a smoking history of at least 10 pack-years will be selected in order to immunologically match the COPD population as much as possible. Literature data indeed suggest that alterations of the immune system start early on in smokers, before the COPD disease is recognised [Barcelo, 2008; Droemann, 2005; Takanashi, 1999]. Several formulations of a vaccine containing the NTHi antigens (10 or 30 µg) either non-adjuvanted or combined with different adjuvants (aluminium [Al], adjuvant system [AS]01_E and $AS04_C$) were already evaluated in two previous Phase 1 clinical trials (NTHI-002 in healthy adults aged 18 - 40 years and NTHI-003 in current and former healthy smokers of 50-70 years old). The investigational vaccines were well-tolerated, with an acceptable safety and reactogenicity profile. These studies allowed the dose selection of the NTHi antigens (10 µg) and the adjuvant system ($AS01_E$) evaluated for the first time in moderate and severe COPD patients aged 40-80 years in the Phase 2 study NTHI-004. The safety, reactogenicity and immunogenicity of different formulations of the NTHi-Mcat investigational vaccine have been evaluated in the Phase 1 study in healthy adults aged

18-40 years and in current and former smokers aged 50-70 years (study NTHI MCAT-001). Based on results obtained up to 30 days post-Dose 2 from this study, the $AS01_E$-adjuvanted formulation containing 10 µg of NTHi proteins PD and PE-PilA and 3.3 µg of UspA2 has been selected for evaluation in the current NTHI MCAT-008 study. The current study will evaluate the impact of a 3rd dose (following a 0-2 month vaccination schedule), either given at 6 months or at 12 months after the first dose. The primary aim is to assess the safety of the additional dose. We will also investigate how the two schedules improve the persistence of antibody response.

- Rationale for the study design

Previous studies in the COPD project have evaluated a 2-dose vaccination schedule. The current study will evaluate the safety and immunogenicity of 3 doses of the investigational vaccine. Adults aged 40 to 80 years with a smoking history of at least 10 pack-years, will receive 2 doses of the NTHi-Mcat investigational vaccine at 0 and 2 months in both study arms. Following these 2 doses, one study arm will receive a 3rd dose of the investigational NTHi-Mcat vaccine at 6 months and a placebo control at 12 months (**Schedule 1**) and the other study arm will receive a placebo control at 6 months and a 3rd dose of the investigational NTHi-Mcat vaccine at 12 months (**Schedule 2**).

- Rationale for the use of placebo

The placebo dose is included in the NTHI MCAT-008 study in order to preserve the blind in the evaluation of the two vaccination schedules.

Objectives

Primary

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

Secondary

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

Tertiary

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

Study design

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

  Refer to glossary of terms for the definition of PCD.
- End of Study (EoS): Last testing results released of samples collected at Visit 10 (Day 721).

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

Synopsis Table 1 Study groups and epochs foreseen in the study

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

Synopsis Table 2 Study groups and treatment foreseen in the study

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

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

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	open

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

  Refer to Section 5.6.18 for study procedures to be considered during special circumstances.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF), Diary Cards and Phone contacts.

- Safety monitoring: Safety evaluations by the Safety Review Team (SRT) (blinded). Refer to section 8.10 for description of safety monitoring.

Number of subjects

Approximately 100 eligible adult subjects aged 40 to 80 years having a significant smoking history (≥ 10 pack-years) per study group (i.e. ~200 subjects in total).

Endpoints

Primary

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) reported within 7 days (Day 1 – Day 7) after each vaccination, within each vaccination schedule.
- Unsolicited adverse events.
  - Occurrence of each unsolicited AE reported within 30 days (Day 1 – Day 30) after any vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, within each vaccination schedule.
- Serious adverse events.
  - Occurrence of any serious adverse events reported from Day 1 (Visit 1) up to and including Day 541 (Visit 9), within each vaccination schedule.
- Potential Immune-mediated diseases (pIMDs).
  - Occurrence of pIMDs reported from Day 1 (Visit 1) up to and including Day 541 (Visit 9), within each vaccination schedule.

Secondary

- Serious Adverse Events.
  - Occurrence of any serious adverse events reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.
- Potential Immune-mediated diseases (pIMDs).
  - Occurrence of pIMDs reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.
- Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations, as measured by ELISA, at Day 1, Day 91,

Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.

- Anti-PD, anti-PE, anti-PilA and anti-UspA2 seropositivity, as measured by ELISA, at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.
- NTHi-specific and Mcat-specific cell-mediated immune responses as measured by flow cytometry ICS **/**frequency of specific CD4+ T-cells expressing two or more markers, such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), and CD40 ligand (CD40L)], at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391, in a sub-cohort of subjects and within each vaccination schedule.

Tertiary

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

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LIST OF ABBREVIATIONS

(Amended 26 May 2020)

AE:	Adverse Event
AECOPD:	Acute Exacerbation of COPD
Al:	Aluminium
ANCOVA:	Analysis of covariance
AS01$_E$:	Adjuvant System 01$_E$
CD:	Cluster of Differentiation
CDC:	Centers for Disease Control
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CMI:	Cell-Mediated Immunity
COPD:	Chronic Obstructive Pulmonary Disease
COVID-19	***Coronavirus Disease 2019***
CRDL:	Clinical Research & Development Lead
eCRF:	electronic Case Report Form
EDD:	Estimated Date of Delivery
EGA:	Estimated Gestational Age
ELISA:	Enzyme-linked immunosorbent assay
eTDF:	Electronic Temperature excursion Decision Form
EoS:	End of Study
ES:	Exposed Set
FAS:	Full Analysis Set
GCP:	Good Clinical Practice
GM:	Geometric Mean

GMC:	Geometric Mean Concentration
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
GSK:	GlaxoSmithKline
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
ICS:	Intracellular Cytokine Staining
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IFN-γ:	Interferon gamma
IgG:	Immunoglobulin G
IL:	Interleukin
IM:	Intramuscular
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
IRB:	Institutional Review Board
LAR:	Legally Acceptable Representative
LMP:	Last Menstrual Period
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MATEX:	MATerial EXcellence
Mcat:	*Moraxella catarrhalis*
MedDRA:	Medical Dictionary for Regulatory Activities
mg:	Milligram
ml:	Millilitre

NTHi:	Non-typeable *Haemophilus influenzae*
PBMC:	Peripheral Blood Mononuclear Cell
PCD:	Primary Completion Date
PD:	Protein D
PE:	Protein E
PilA:	Type IV pili subunit
pIMD:	Potential Immune-Mediated Disease
PPS:	Per Protocol Set
PT:	Preferred Term
SAE:	Serious Adverse Event
SAS:	Statistical Analysis Software
SBIR:	Randomisation System on Internet
SRT:	Safety Review Team
TNF-α:	Tumour Necrosis Factor alpha
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
UspA2:	Ubiquitous surface protein A2
WHO:	World Health Organisation
µL:	Microliter

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,
- Combined estrogen and progesterone oral contraceptives,
- Injectable progestogen,
- Implants of etenogestrel or levonorgestrel,
- Contraceptive vaginal ring,
- Percutaneous contraceptive patches,
- Intrauterine device or intrauterine system,
- Male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- Male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products,

	this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Alcoholism:	Alcoholism, also known as dependency on alcohol or alcohol addiction, is a chronic disease. The signs and symptoms of alcoholism include: • A strong craving for alcohol. • Continued use despite repeated physical, psychological, or interpersonal problems. • The inability to limit drinking.
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 5.3 for details on observer-blinded studies).
Current smoker:	A person who is currently smoking or who has stopped smoking within 6 months before study start.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.
Epoch:	An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data

	collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Sections 6.6.2 and 10.5 for details on criteria for evaluability).
Former smoker:	A person who stopped smoking for at least 6 months at the time of study start.
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.

Pack-years of smoking:	Pack-years is a quantification of cigarette smoking, a way to measure the total amount a person has smoked in the course of his/ her lifetime. The number of pack-years is calculated as follows: (average number of *cigarettes* smoked per day x number of years smoked)/ 20 E.g. a smoking history of 10 pack-years means having smoked 20 cigarettes per day for 10 years, or having smoked 10 cigarettes per day for 20 years. *Note*: For the purpose of this study, pipe and/or cigar use (including cigarillos) 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 all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
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.
Study vaccine/product	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/ product /placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.

Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule,…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine 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.
Treatment number:	A number identifying a treatment to a subject, according to 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. COPD: an introduction

Chronic Obstructive Pulmonary Disease (COPD), a common preventable disease, is characterised by persistent airflow limitation that is usually progressive. The airflow limitation is associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles of gases. The most important environmental risk factor for COPD is tobacco smoking, even though other factors, such as occupational exposure, may also contribute to the development of the disease [GOLD, 2017]. It is a multi-component disease that manifests as an accelerated decline in lung function, with symptoms such as breathlessness on physical exertion, deteriorating health status and exacerbations.

The prevalence of COPD is increasing. Worldwide, COPD (GOLD grade II and above) affects 10.1±4.8% of the population ≥40 years of age [Buist, 2007]. COPD is most prevalent in adults/elderly with a history of smoking [Mannino, 2002]. It is the fourth leading cause of chronic morbidity and mortality in the United States and the first in terms of disease burden in China. According to the World Health Organisation (WHO), COPD is expected to be the third cause of death worldwide by 2020 [Rabe, 2007].

Acute exacerbations and comorbidities contribute to the overall disease severity in individual COPD patients. An acute exacerbation of COPD (AECOPD) is defined as an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [GOLD, 2017]. AECOPD additionally increase morbidity and mortality, lead to faster decline in lung function, poorer functional status, and have a significant impact on healthcare systems worldwide [Sapey, 2006]. 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; Wilkinson, 2017]. In COPD patients, acquisition of new bacterial strains is believed to be an important cause of AECOPD [Sethi, 2002]. Although estimates vary widely, Non-Typeable *Haemophilus influenzae* (NTHi) appears to be the main bacterial pathogen associated with AECOPD (11-38%), followed by *Moraxella catarrhalis* (Mcat) (3-25%) and *Streptococcus pneumoniae* (4-9%) [Alamoudi, 2007; Bandi, 2003; Beasley, 2012; Hutchinson, 2007; Ko, 2007; Larsen, 2009; Murphy, 2005; Papi, 2006; Rosell, 2005; Sethi, 2002; Sethi, 2008; Wilkinson, 2006]. A prospective, observational cohort study in patients with COPD aged 40-85 is ongoing to assess how changes in the COPD airway microbiome contribute to the incidence and severity of AECOPD [Bourne, 2014]. Molecular diagnostic and typing techniques are used to describe the dynamics of airway infection during AECOPD and stable disease, and associations with clinical outcome. These results will increase our understanding of the contribution of pathogens to AECOPD.

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 manage or treat COPD, some with a positive impact on the AECOPD rate. However, a need for further novel interventions remains because current approaches are not completely effective, even when targeted and used optimally.

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

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

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

1.1.3. GSK Biologicals' NTHi-Mcat investigational vaccine

GlaxoSmithKline (GSK) Biologicals is developing a new NTHi-Mcat investigational vaccine against diseases caused by NTHi and Mcat. The investigational vaccine that will be evaluated in the present study is an adjuvanted multi-component vaccine consisting of conserved surface proteins from NTHi and Mcat. Three NTHi proteins have been selected: Protein D (PD), as a free recombinant protein and Protein E (PE) and PilA protein, as a recombinant fusion protein named PE-PilA. The selected Mcat antigen is the UspA2.

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

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

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

The purpose of this Phase 2 study is to evaluate two vaccine schedules of the investigational NTHi-Mcat vaccine.

As the prevalence of COPD increases with age and as age has an influence on both the immunogenicity and reactogenicity of a vaccine, subjects 40–80 years old will be enrolled. As cigarette smoking is the most commonly encountered risk factor for COPD, adults with a smoking history of at least 10 pack-years will be selected in order to immunologically match the COPD population as much as possible. Literature data indeed suggest that alterations of the immune system start early on in smokers, before the COPD disease is recognised [Barcelo, 2008; Droemann, 2005; Takanashi, 1999].

Several formulations of a vaccine containing the NTHi antigens (10 or 30 µg) either non-adjuvanted or combined with different adjuvants (aluminium [Al], adjuvant system [AS]01_E and $AS04_C$) were already evaluated in two previous Phase 1 clinical trials (NTHI-002 in healthy adults aged 18 - 40 years and NTHI-003 in current and former healthy smokers of 50-70 years old). The investigational vaccines were well-tolerated, with an acceptable safety and reactogenicity profile. These studies allowed the dose selection of the NTHi antigens (10 µg) and the adjuvant system ($AS01_E$) evaluated for the first time in moderate and severe COPD patients aged 40-80 years in the Phase 2 study NTHI-004.

The safety, reactogenicity and immunogenicity of different formulations of the NTHi-Mcat investigational vaccine have been evaluated in the Phase 1 study in healthy adults aged 18-40 years and in current and former smokers aged 50-70 years (study NTHI MCAT-001). Based on results obtained up to 30 days post-Dose 2 from this study, the $AS01_E$-adjuvanted formulation containing 10 µg of NTHi proteins PD and PE-PilA and 3.3 µg of UspA2 has been selected for evaluation in the current NTHI MCAT-008 study. The current study will evaluate the impact of a 3rd dose (following a 0-2 month vaccination schedule), either given at 6 months or at 12 months after the first dose. The primary aim is to assess the safety of the 3rd dose. We will also investigate how these two schedules improve the persistence of antibody response.

1.2.2. Rationale for the study design

Previous studies in the COPD project have evaluated a 2-dose vaccination schedule. The current study will evaluate the safety and immunogenicity of 3 doses of the investigational vaccine. Adults aged 40 to 80 years with a smoking history of at least 10 pack-years, will receive 2 doses of the NTHi-Mcat investigational vaccine at 0 and 2 months in both study arms. Following these 2 doses, one study arm will receive a dose of the investigational NTHi-Mcat vaccine at 6 months and a placebo at 12 months (**Schedule 1**) and the other study arm will receive a placebo at 6 months and a dose of the investigational NTHi-Mcat vaccine at 12 months (**Schedule 2**).

1.2.3. Rationale for the use of placebo

The placebo dose is included in the NTHI MCAT-008 study in order to preserve the blind in the evaluation of the two vaccination schedules.

1.3. Benefit: Risk Assessment

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

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

1.3.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
NTHi-Mcat investigational vaccine		
Theoretical risk of acquiring a vaccine-induced autoimmune disease after vaccination	No confirmed signals related to this potential risk have been identified during the preclinical and clinical programs so far.	Close monitoring of potential immune-mediated diseases in clinical development programs using adjuvant systems. The potential risk for events of possible autoimmune aetiology to occur is mentioned in the Informed Consent Form (ICF).
Study Procedures		
Risk of blood sampling	Blood sampling associated risk of syncope, dizziness, infection at the site after or during venepuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health (see section 5.6.14).

1.3.2. Benefit Assessment

- Contribution to the process of developing of a vaccine against AECOPD.
- Medical evaluations/assessments associated with this study (i.e. physical examination).

1.3.3. Overall Benefit: Risk Conclusion

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

2. OBJECTIVES

2.1. Primary objective

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

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

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

Refer to Section 10.2 for the definition of the secondary endpoints.

2.3. Tertiary objectives

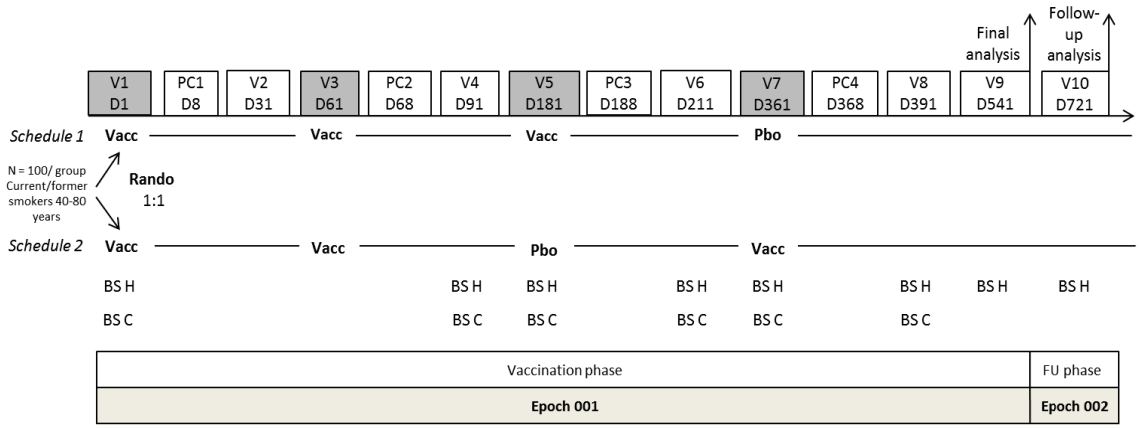
- To explore the T helper profile to the PD-, PE-, PilA-, UspA2 -specific CD4+/ CD8+ T cell responses.
- To evaluate the cellular immunogenicity (CD8+ T cell response) of the NTHi-Mcat investigational vaccine.
- To collect blood samples for assay development/validation and/or for additional evaluation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

Refer to Section 10.3 for the definition of the tertiary endpoints and to section 10.11.1 for the reporting of tertiary endpoint results.

3. STUDY DESIGN OVERVIEW

(Amended 26 May 2020)

Figure 1 Study design overview



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

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

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

Refer to glossary of terms for the definition of PCD.

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

Refer to glossary of terms for the definition of EoS.

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

Table 1 Study groups and epochs foreseen in the study

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

Table 2 Study groups and treatment foreseen in the study

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

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

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	open

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

Refer to Section 5.6.18 for study procedures to be considered during special circumstances.

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

4. STUDY COHORT

4.1. Number of subjects/centres

This will be a multi-centre study.

The target is to enrol 100 eligible adult subjects aged 40 to 80 years having a significant smoking history (≥ 10 pack-years) per study group (i.e. ~200 subjects in total). Refer to Section 10.4 for a detailed description of the criteria used in the estimation of the sample size.

Approximately 20% of the subjects (~40 subjects in total) will be part of a **sub-cohort for CMI** analysis. An additional blood sample will be taken from these subjects at specified timepoints (Visits 1 [Day 1], 4 [Day 91], 5 [Day 181], 6 [Day 211], 7 [Day 361] and 8 [Day 391]). The CMI sub-cohort will be selected from sites able to process the blood samples according to GSK procedures for peripheral blood mononuclear cell (PBMC) preparation.

Table 4 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
Sub-cohort for CMI	At specific timepoints (Visit 1, 4, 5, 6, 7 and 8), 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)

4.2. Inclusion criteria for enrolment

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

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the Diary Cards, completion of blood draws, return for follow-up visits).
- Written informed consent obtained from the subject prior to performing any study specific procedure.
- A male or female between, and including, 40 and 80 years of age at the time of the first vaccination.

- Current or former smoker with a cigarette smoking history of ≥ 10 pack-years.

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

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

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

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

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

4.3. Exclusion criteria for enrolment

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

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

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day -29 to Day 1), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first and ending 30 days after the last dose of vaccine administration, with the exception of any influenza or pneumococcal vaccine which may be administered ≥ 15 days preceding or following any study vaccine dose.

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination with any vaccine containing NTHi and/or Mcat antigens.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of or current autoimmune disease.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 37.5°C. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first dose of study vaccine or planned administration during the study period.
- Pregnant or lactating female.
- Current alcoholism and/or drug abuse.

  Please refer to the glossary of terms for the definition of alcoholism.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- Diagnosed with a respiratory disorder (e.g. asthma, COPD, sarcoidosis, tuberculosis, bronchiectasis, lung fibrosis, pulmonary embolism, pneumothorax, or physician confirmed lung cancer).
- Has significant disease (including significant neurological or psychological disorders), in the opinion of the investigator, likely to interfere with the study and/or likely to cause death within the study duration.
- Malignancies within previous 5 years (excluding non-melanoma skin cancer) or lymphoproliferative disorders.
- Any other condition that the investigator judges may interfere with study findings.

5. CONDUCT OF THE STUDY

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

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

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

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

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

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

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

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

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

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

5.2. Subject identification and randomisation

5.2.1. 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.

5.2.2. Randomisation of treatment

5.2.2.1. Randomisation of supplies

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

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Study group allocation

The target will be to enrol approximately 200 eligible subjects who will be randomly assigned to two study groups in a (1:1) ratio (approximately 100 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on internet (SBIR).

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for the first dose.

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

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

5.2.2.2.2. Treatment number allocation for subsequent doses

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

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

5.3. Method of blinding

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

Data of Epoch 1 will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity) will all be unaware of whether vaccine or placebo was administered**.**

Data of Epoch 2 (long-term safety follow-up) will be collected in an open manner, as a clinical study report will be developed with all completed and cleaned data collected up to and including Visit 9 (Day 541 - Primary Completion Date).

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 (e.g. study nurse) 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.

5.4. 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.

5.5. Outline of study procedures

(Amended 26 May 2020)

Table 5 List of study procedures

Epoch	*Epoch 001*													*Epoch 002*
Type of contact	**Visit 1**	**Phone contact 1**	**Visit 2**	**Visit 3**	**Phone contact 2**	**Visit 4**	**Visit 5**	**Phone contact 3**	**Visit 6**	**Visit 7**	**Phone contact 4**	**Visit 8**	**Visit 9**	**Visit 10** [i]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**	**Day 181**	**Day 188**	**Day 211**	**Day 361**	**Day 368**	**Day 391**	**Day 541**	**Day 721** [h]
Sampling timepoints	**Pre-Vacc I**					**Post-Vacc II**	**Pre-Vacc III**		**Post-Vacc III**	**Pre-Vacc IV**		**Post-Vacc IV**	**Post-Vacc IV**	**Post-Vacc IV**
Informed consent	●													
Check inclusion/exclusion criteria	●													
Collect demographic data	●													
Medical history	●													
Smoking status	●												●	
Smoking exposure history (ATS-DLD-78A questionnaire)	●													
Measure/record height and weight	●											O [a]	O [a]	
Physical examination	●		O [a]	O [a]		O [a]	O [a]		O [a]	O [a]		O [a]	●	●
Urine pregnancy test [b]	●			●			●			●				
Check contraindications to vaccination	O			O [d]			O [d]			O [d]				
Pre-vaccination body temperature	●			●			●			●				
Vaccines														
Study group and treatment number allocation	O			O			O			O				
Vaccine administration	●			●			●			●				
60 minutes post-injection assessment	●			●			●			●				
Laboratory Assays														
Blood sampling for antibody determination (~20 ml)	● [f]					●	● [f]		●	● [f]		●	●	● *[h]*
Blood sampling for CMI response (~40 ml) [c]	● [f]					●	● [f]		●	● [f]		●		

Epoch	*Epoch 001*													*Epoch 002*
Type of contact	**Visit 1**	**Phone contact 1**	**Visit 2**	**Visit 3**	**Phone contact 2**	**Visit 4**	**Visit 5**	**Phone contact 3**	**Visit 6**	**Visit 7**	**Phone contact 4**	**Visit 8**	**Visit 9**	**Visit 10** [i]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**	**Day 181**	**Day 188**	**Day 211**	**Day 361**	**Day 368**	**Day 391**	**Day 541**	**Day 721** [h]
Sampling timepoints	**Pre-Vacc I**					**Post-Vacc II**	**Pre-Vacc III**		**Post-Vacc III**	**Pre-Vacc IV**		**Post-Vacc IV**	**Post-Vacc IV**	**Post-Vacc IV**
Safety assessments														
Distribution of Subject Card	O													
Distribution of Diary cards	O			O			O			O				
Return and review of Diary cards			O			O			O			O		
Diary card transcription			●			●			●			●		
Record any concomitant medications/vaccinations associated with an AE	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions [e] [g]		●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of AEs [e] [g]		●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of SAEs [e] [g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of pIMDs [e]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of pregnancies [e]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Study Conclusion													●	●

Note: The double-line border following Day 541 indicates the final analysis which will be performed on all data (i.e. data that are as clean as possible) obtained up to that timepoint.
Vacc: vaccination.

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

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

[a] This procedure will be performed only if deemed necessary by the Investigator or delegate.

[b] Only for women of childbearing potential.

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

[d] Refer to Section 6.5 for more details on study procedures for subjects meeting contraindications to subsequent vaccination before administration of vaccine Dose 2, 3 and 4.

[e] Please refer to Section 8.3 for recording periods of local and general solicited AEs, unsolicited AEs, SAEs, (S)AEs leading to study withdrawal, SAEs related to study vaccine(s)/product(s), intercurrent medical conditions, pIMDs and pregnancies.

[f] Blood sampling must occur prior to vaccination.

[g]. If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs or SAEs (refer to Section 8.1 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 16

[h]. The timepoints for Visit 10 and for blood sampling may change according to extended intervals. Refer to Section 5.6.18 for study procedures to be considered during special circumstances and Table 6 for details on visit intervals

[i] Visit 10 may be a telephone contact during special circumstances. Refer to Section 5.6.18 for study procedures to be considered during special circumstances.

Whenever possible, the investigator should arrange study visits within the interval described in Table 6.

Table 6 Intervals between study visits

(Amended 26 May 2020)

Interval	Optimal length of interval	Allowed interval
Visit 1 → Phone contact 1	7 days	7 - 9 days
Visit 1 → Visit 2	30 days	30 - 45 days
Visit 1 → Visit 3	60 days	60 - 75 days[1]
Visit 3 → Phone contact 2	7 days	7 - 9 days
Visit 3 → Visit 4	30 days	30 - 45 days [1]
Visit 3 → Visit 5	120 days	120 - 150 days [1]
Visit 5 → Phone contact 3	7 days	7 - 9 days
Visit 5 → Visit 6	30 days	30 - 45 days [1]
Visit 5 → Visit 7	180 days	180 – 210 days [1]
Visit 7 → Phone contact 4	7 days	7 – 9 days
Visit 7 → Visit 8	30 days	30 – 45 days [1]
Visit 7 → Visit 9	180 days	180 – 210 days [1]
Visit 7 → Visit 10	360 days	360 – 390 days ***(+120 days under special circumstances)^[1]***

[1] Subjects will not be eligible for inclusion in the per-protocol set (PPS) for analysis of immunogenicity if the study visit is performed outside this interval.

^ Refer to Section 5.6.18 for study procedures to be considered during special circumstances. Impact on the per protocol set for immunogenicity will be determined on a case by case basis

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. Collect demographic data

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

5.6.4. Medical history

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

5.6.5. 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.

5.6.6. Smoking exposure history

Smoking history will be obtained by means of a self-administered questionnaire (which will be part of the ATS-DLD-78A questionnaire) provided to the subjects, in which they will give answers about their smoking history, including duration (number of years) and number of cigarettes smoked.

Please refer to the SPM for more details on questionnaire.

From the information obtained via the questionnaire, calculate the pack-years using the following calculation (also refer to the glossary of terms for the definitions of pack-years) Please note that pipe and/or cigar use should not be used to calculate pack-year history:

$$\text{Total pack-years} = \frac{\text{Average no. cigarettes smoked / day x no. years of smoking}}{20}$$

All data will be recorded in the subject's eCRF.

5.6.7. Measure/record height and weight

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

5.6.8. Physical examination

At Visit 1, Visit 9 and Visit 10, 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 (including vital signs) at Visit 2 up to and including Visit 8 will be performed only if deemed necessary by the Investigator or delegate.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the allowed interval for this visit (see Table 6).

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.

5.6.9. Urine Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the urine 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.

5.6.10. Check contraindications to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Section 6.5 for more details.

5.6.11. Assess pre-vaccination body temperature

The oral or axillary body temperature of all subjects needs to be measured prior to any study vaccine administration. If the subject has fever (fever is defined as temperature ≥ 37.5°C) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 6).

5.6.12. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.13. Study Vaccine administration

After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) preferably in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine 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 (refer to Table 6).

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.

5.6.14. 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.

5.6.14.1. Blood sampling for immune response assessments

(Amended 26 May 2020)

Blood samples will be taken during certain study visits as specified in Table 5 (List of Study Procedures). Blood sampling should occur prior to vaccine administration on days where vaccines are administered.

Blood samples for humoral immunogenicity

A volume of approximately 20 mL of whole blood should be drawn from all subjects for each analysis of humoral immune response at each pre-defined timepoint (Visit 1, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9 and Visit 10)*. After whole blood processing into serum, serum samples should be kept at ≤–20°C until shipment. Refer to the SPM and Central Laboratory manual for more details on sample storage conditions.

**** Refer to Section 5.6.18 for study procedures to be considered during special circumstances.***

Blood samples for CMI

A volume of approximately 40 mL of whole blood should be drawn from all subjects included in the immunogenicity sub-cohort for analysis of cell-mediated immune (CMI) response at each pre-defined timepoint (Visit 1, Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8). The samples should be kept at room temperature and should be shipped as soon as possible (maximum 8 hours after whole blood collection) so that the CMI laboratory can start cell separation processing within 24 hours of collection. Refer to the SPM and Central Laboratory manual for more details on sample storage conditions.

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

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.6.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.7.

5.6.16. Distribution of Subject Card

For information regarding the Subject Card, please refer to Section 8.9.

5.6.17. Recording of AEs, SAEs, pregnancies and pIMDs

(Amended 26 May 2020)

- Refer to Section 8.3 for procedures for the investigator to record AEs, SAEs, pregnancies and pIMDs. Refer to Section 8.4 for guidelines and how to report SAE, pregnancy and pIMD reports to GSK Biologicals. Refer to the telephone script for more details on what should be collected during the Phone contacts.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, paper diary cards will be provided to the subject. The subject will be instructed to measure and record the oral or axillary body temperature, any solicited local/general (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (occurring on the day of vaccination and during the next 29 days after each vaccination). The subject will be instructed to return the completed diary card to the investigator at the next study visit.
- Collect and verify completed diary cards during discussion with the subject on Visit 2, Visit 4, Visit 6, and Visit 8.
- 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 in English.

For Epoch 002, this includes the assessment of COVID-19 cases in accordance with the WHO definition. Refer to Section 5.6.18 and 8.3.1 for details.

5.6.18. Study procedures during special circumstances

(Amended 26 May 2020)

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants (still participating in the study) for Visit 10:

- ***If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 6), then the interval may be extended up to a maximum length of 120 days (i.e. allowed interval for Visit 10 = 360 to 390 days +120 days under special circumstances).***
- ***In case, a physical visit to the clinic is not possible in any circumstances even with the extended interval, safety follow-up may be made by a telephone call or other means of virtual contact, if appropriate. The telephone call/ mode of virtual contact will be considered equivalent to study conclusion visit.***

5.6.19. Study conclusion

The investigator will:

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

5.7. Biological sample handling and analysis

Please refer to the SPM and 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).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

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

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

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

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

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals and/or a central laboratory, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 10.5 for the definition of cohorts to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals and/or a central laboratory does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM and to the Central Laboratory investigator manual.

5.7.2. Biological samples

(Amended 26 May 2020)

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoint	Sub-cohort
Blood for humoral immunogenicity	~20	ml	• Visit 1 (Day 1) • Visit 4 (Day 91) • Visit 5 (Day 181) • Visit 6 (Day 211) • Visit 7 (Day 361) • Visit 8 (Day 391) • Visit 9 (Day 541) • Visit 10 (Day 721)**	All enrolled subjects
Blood for CMI	~40	ml	• Visit 1 (Day 1) • Visit 4 (Day 91) • Visit 5 (Day 181) • Visit 6 (Day 211) • Visit 7 (Day 361) • Visit 8 (Day 391)	Sub-cohort for CMI*

*Refer to Section 4.1 for sub-cohort description.
***** Refer to Section 5.6.18 for study procedures to be considered during special circumstances and Table 6 for details on extended visit interval.***

5.7.3. Laboratory assays

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

Humoral antibody responses

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

Table 8 Humoral Immunity (Antibody determination)

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

EU/mL = ELISA unit per millilitre

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

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

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

Cell-mediated immune responses

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

Table 9 Cell-mediated Immunity (CMI) using flow cytometry

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

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

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

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

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

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

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

(Amended 26 May 2020)

Table 10 Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Vacc I	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		CMI sub-cohort*	~40	Specific CD4+/CD8+ T-cells
Visit 4 (Day 91)	Post-Vacc II	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		CMI sub-cohort*	~40	Specific CD4+/CD8+ T-cells
Visit 5 (Day 181)	Pre-Vacc III	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		CMI sub-cohort*	~40	Specific CD4+/CD8+ T-cells
Visit 6 (Day 211)	Post-Vacc III	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		CMI sub-cohort*	~40	Specific CD4+/CD8+ T-cells
Visit 7 (Day 361)	Pre-Vacc IV	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		CMI sub-cohort*	~40	Specific CD4+/CD8+ T-cells
Visit 8 (Day 391)	Post-Vacc IV	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
		CMI sub-cohort*	~40	Specific CD4+/CD8+ T-cells
Visit 9 (Day 541)	Post-Vacc IV	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
Visit 10 (Day 721)**	Post-Vacc IV	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2

*Approximately 20% of the subjects in each group will be part of a sub-cohort for CMI analysis.
***** Refer to Section 5.6.18 for study procedures to be considered during special circumstances and Table 6 for details on extended visit interval.***

5.7.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the antigens used in the candidate vaccine.

6. STUDY VACCINES AND ADMINISTRATION

6.1. 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 vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

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

Table 11 Study vaccines

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

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

6.2. Storage and handling of study vaccines

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

Temperature excursions must be reported in degree Celsius.

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

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

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

6.3. Dosage and administration of study vaccines

Table 12 Dosage and administration

Type of contact and timepoint	Study group	Treatment name	Volume to be administered	Route [1]	Site		
					Location	Directionality[2]	Laterality[3]
Visit 1 (Day 1)	Schedule 1	10-10-3/AS01E	0.5 ml	IM	Deltoid	Upper	Non-dominant
	Schedule 2						
Visit 3 (Day 61)	Schedule 1	10-10-3/AS01E	0.5 ml	IM	Deltoid	Upper	Non-dominant
	Schedule 2						
Visit 5 (Day 181)	Schedule 1	10-10-3/AS01E	0.5 ml	IM	Deltoid	Upper	Non-dominant
	Schedule 2	Placebo					
Visit 7 (Day 361)	Schedule 1	Placebo	0.5 ml	IM	Deltoid	Upper	Non-dominant
	Schedule 2	10-10-3/AS01E					

[1] Intramuscular (IM)
[2] Directionality is a qualifier for further detailing the location of the vaccine administration (e.g. Upper, Lower)
[3] The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

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

6.4. 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.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of NTHi-Mcat vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.5).

- Anaphylaxis following the administration of vaccine.
- Pregnancy (see Section 8.2.1).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Current auto-immune disease.
- Malignancy (excluding non-melanotic skin cancer and carcinoma in situ of the cervix, if considered cured) or lymphoproliferative disorder.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 8.1.5.1 for the definition of pIMDs.

The following events constitute contraindications to administration of NTHi-Mcat vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines at the discretion of the investigator.

6.6. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator or delegate should question the subject about any medications/products taken and vaccinations received by the subject.

6.6.1. Recording of concomitant medications/products and concomitant vaccinations

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

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

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.5°C]. The preferred location for measuring temperature in this study will be the oral cavity or the axilla.
- Any concomitant medications/products/vaccines listed in Section 6.6.2.
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

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

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 10.5 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending at 30 days after the last dose of vaccine administration*, with the exception of any influenza or pneumococcal vaccine which may be administered ≥ 15 days preceding or following any study vaccine dose.

* 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 and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

- Immunoglobulins and/or any blood products administered during the study period.
- Drug and/or alcohol abuse.

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

At each study visit subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition that may lead to elimination from per-protocol analyses. If it is the case, the condition(s) must be recorded in the eCRF.

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

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

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

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

8.1. Safety definitions

8.1.1. 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:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study 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 study 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 8.1.3. 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.
- 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.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

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

c. Requires hospitalisation or prolongation of existing hospitalisation,

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

that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, OR

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

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

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

8.1.3. 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) and unsolicited AEs occurring during a 30-day follow-up period after each vaccination (i.e. the day of vaccination and the 29 subsequent days), will be reported via diary cards. In addition, subjects will be asked at Phone contacts if there were any safety concerns in the last 7 days; this information will be recorded via the appropriate section of the eCRF.

8.1.3.1. Solicited local (injection-site) adverse events

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

Table 13 Solicited local adverse events

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

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 14 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms†
Headache
Myalgia
Chills

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

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

8.1.4. 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 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

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

8.1.5. Adverse events of specific interest

8.1.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 15. In case of further updates to the pIMDs list, the investigators will be notified in a written communication. No further protocol amendments will be released.

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 15 List of potential immune-mediated diseases

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

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

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

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

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

8.2.1. 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 8.4.1 and 8.4.3:

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

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

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine will be reported to GSK Biologicals as described in Section 8.4.3. 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.

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

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

(Amended 26 May 2020)

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

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at the last study visit. See Section 8.4 for instructions on reporting of SAEs.

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

For Epoch 002, this includes the assessment of COVID-19 cases in accordance with the current WHO definition. Cases should be categorised as AEs (unsolicited or AEs leading to withdrawal) or SAEs (refer to Section 8.1 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 16.

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

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end at last study visit. See section 8.4 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end at the last study visit. See section 8.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 16.

Table 16 Reporting periods for collecting safety information

Event	Visit 1 Dose 1	6 d post Dose 1	29 d post Dose 1	Visit 3 Dose 2	6 d post Dose 2	29 d post Dose 2	Visit 5 Dose 3	6 d post Dose 3	29 d post Dose 3	Visit 7 Dose 4	6 d post Dose 4	29 d post Dose 4	Study conclusion
Timepoint	**Day 1**	**Day 7**	**Day 30**	**Day 61**	**Day 67**	**Day 90**	**Day 181**	**Day 187**	**Day 210**	**Day 361**	**Day 367**	**Day 390**	**Day 721**
Solicited local and general AEs													
Unsolicited AEs													
AEs/SAEs leading to withdrawal from the study**													
SAEs **													
SAEs related to study participation or concurrent GSK medication/vaccine													
Pregnancies													
pIMDs													
Intercurrent medical conditions leading to exclusion per protocol**													

* i.e. consent obtained. The double-bordered lines indicate timings of vaccination.

** ***During Epoch 002, if a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as (S)AEs leading to withdrawal) or SAEs (refer to Section 8.1 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the defined time period.***

8.3.2. 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 16. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.3. Evaluation of adverse events and serious adverse events

8.3.3.1. 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.

8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

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

Table 17 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	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Chills	0	None
	1	Chills that are easily tolerated
	2	Chills that interfere with normal activity
	3	Chills that prevent normal activity

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

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

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

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

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

0: < 37.5°C
1: 37.5°C to 37.9°C
2: 38.0°C to 38.9°C
3: ≥ 39.0°C

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

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

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

8.3.3.2.2. Assessment of causality

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

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

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

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

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

YES	:	There is a reasonable possibility that the study 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 8.1.2), 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).

8.3.3.3. 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).

8.3.3.4. 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.

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

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

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 18, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 18, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 18, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 18 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

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

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

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

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

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

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

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

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

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

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

8.4.4. 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.

8.4.5. Reporting of pIMDs to GSK Biologicals

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the

event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

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

Refer to Section 8.4.3.1 for back-up system in case the electronic reporting system does not work.

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

When additional SAE, pregnancy or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 18.

8.4.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

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

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

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

8.5.1.1. 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 18).

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

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.

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

The investigator will follow subjects:

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

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

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

8.5.2. Follow-up of pregnancies

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

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

8.6. 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 a SAE / pIMDs should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.6).

8.7. Unblinding

GSK Biologicals' policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the study vaccine, 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 8.4.1).

8.8. Emergency unblinding

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

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

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

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

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

8.9. Subject card

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

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

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

8.10. Safety monitoring

8.10.1. Safety Review Team

The project's SRT includes as core members the GSK Biologicals' Central Safety Physician, Epidemiologist, the Clinical Research & Development Lead (CRDL), Clinical Regulatory Affairs representative and the Biostatistician of the project. The SRT is responsible for on-going safety monitoring (blinded) of the entire project and meets on a regular basis (at least once per year). Additional meetings will be convened as required for events requiring urgent review or ad hoc when significant new safety data becomes available as recommended.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

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

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

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

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

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

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

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

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

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

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

9.2.2. Subject withdrawal from study vaccines

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

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

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

10. STATISTICAL METHODS

10.1. Primary endpoints

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) reported within 7 days (Day 1 – Day 7) after each vaccination, within each vaccination schedule.
- Unsolicited adverse events.
  - Occurrence of each unsolicited AE reported within 30 days (Day 1 – Day 30) after any vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, within each vaccination schedule.
- Serious adverse events.
  - Occurrence of any serious adverse events reported from Day 1 (Visit 1) up to and including Day 541 (Visit 9), within each vaccination schedule.
- Potential Immune-mediated diseases (pIMDs).

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

10.2. Secondary endpoints

- Serious Adverse events
  - Occurrence of any serious adverse events reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.
- Potential Immune-mediated diseases (pIMDs).
  - Occurrence of pIMDs reported from Day 541 (Visit 9) up to and including Day 721 (Visit 10), within each vaccination schedule.
- Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations, as measured by ELISA, at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.
- Anti-PD, anti-PE, anti-PilA and anti-UspA2 seropositivity, as measured by ELISA, at Day 1, Day 91, Day 181, Day 211, Day 361, Day 391, Day 541 and Day 721, within each vaccination schedule.
- NTHi-specific and Mcat-specific cell-mediated immune responses as measured by flow cytometry ICS */*frequency of specific CD4+ T-cells expressing two or more markers, such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), and CD40 ligand (CD40L)*/*, at Day 1, Day 91, Day 181, Day 211, Day 361 and Day 391, in a sub-cohort of subjects and within each vaccination schedule.

10.3. Tertiary endpoint

CMI:

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

10.4. Determination of sample size

Primary objective

In this study, a third injection will be given either at 6 months or at 12 months in order to verify the safety of the third dose.

Considering the sample size of 100 in each vaccination schedule, Table 19 illustrates the precision we can get on the percentage of subjects with grade 3 symptoms following a third vaccination.

A sample size of 100 subjects allows a 2-sided 95% confidence interval with a width equal to 0.165 when the sample proportion is equal to 20%, using a simple asymptotic formula.

Table 19 Exact confidence interval for one proportion

% of subjects with a symptom	N=100 subjects		N=90 subjects*	
	Exact 95% Confidence Interval (CI)		Exact 95% Confidence Interval (CI)	
	Lower Limit	Upper limit	Lower Limit	Upper limit
0	0.0	3.6	0.0	4.0
5	1.6	11.3	1.5	11.7
10	4.9	17.6	4.7	18.1
15	8.6	23.5	8.3	24.1
20	12.7	29.2	12.3	29.8
25	16.9	34.7	16.5	35.2
30	21.2	40.0	20.8	40.6
35	25.7	45.2	25.2	45.8
40	30.3	50.3	29.8	50.9
45	35.0	55.3	34.5	55.8
50	39.8	60.2	39.3	60.7
55	44.7	65.0	44.2	65.5
60	49.7	69.7	49.1	70.2
65	54.8	74.3	54.2	74.8
70	60.0	78.8	59.4	79.2
75	65.3	83.1	64.8	83.5
80	70.8	87.3	70.2	87.7

Computation is done using PASS12.
*Considering a 10% drop out rate.

Table 19 gives confidence intervals for observed events for 90 to 100 subjects.

Table 20 shows the probability to observe a rare adverse event (such as a rare serious AE) in the total study population (approximately 200 subjects).

Table 20 Poisson probability to observe at least one event with rare frequency (μ)

N	μ	μ*N	p>0	p≤0
200	0.01	2.0	0.87	0.13
200	0.011	2.2	0.89	0.11
200	0.012	2.4	0.91	0.09
200	0.013	2.6	0.93	0.07
200	0.014	2.8	0.94	0.06
200	0.015	3.0	0.95	0.05
200	0.016	3.2	0.96	0.04
200	0.017	3.4	0.97	0.03
200	0.018	3.6	0.97	0.03
200	0.019	3.8	0.98	0.02
200	0.02	4.0	0.98	0.02
200	0.021	4.2	0.99	0.01
200	0.022	4.4	0.99	0.01
200	0.023	4.6	0.99	0.01
200	0.024	4.8	0.99	0.01
200	0.025	5.0	>0.99	<0.01

Computation is done using SAS 9.2

Assuming 200 subjects exposed (100 subject in each arm), if the incidence to present a serious or severe event is 1.50%, the probability to observe at least 1 event would equal 95%. This probability will be larger if the incidence is larger than 1.5%.

In absence of event, we would assume either than the incidence is lower or that the false-negative risk of an incidence equal or higher than 1.50% is 5% [Hanley, 1983].

Secondary objectives:

Humoral immunogenicity after third dose

The intent of this secondary objective is to evaluate the improvement of the persistence of antibody response at one month after a third injection. An increase in the antibody titres compared to the second dose is expected.

Approximately a 10% drop out is expected for the third dose evaluation (given at 6 months for one arm and at 12 months for the other arm) and thus 90 evaluable subjects are expected to be analysed for the humoral immunogenicity evaluation.

A sample size of 90 evaluable subjects achieves 90% power to detect a difference of 0.256 between the null hypothesis mean of 0.0 and the alternative hypothesis mean with a known standard deviation of 0.83 and with a significance level (alpha) of 0.05 using a one-sided one-sample t-test.

CMI immunogenicity after third dose

This second secondary objective aims to investigate on the cellular immunogenicity in a subset of 20 subjects per arm (40 subjects in total).

CMI will be evaluated as frequency of CD4+ T-cells expressing at least two different markers, when stimulated by each antigen PD, PE, PilA and UspA2.

No inferential analysis is planned for CMI data and thus 40 subjects are considered to be sufficient for the purpose to report mean, median, min, max, Q1 and Q3 and represent them via boxplot.

10.5. Cohorts for Analyses

The following study cohorts will be evaluated.

10.5.1. Exposed set

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

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

10.5.2. Full Analysis Set

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

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

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

10.5.3. Per-protocol set for analysis of immunogenicity

(Amended 26 May 2020)

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

- Who met all eligibility criteria.
- For whom the administration of the vaccines was according to protocol.
- Who complied with the vaccination schedule, as specified in Table 12 and Table 6.
- Who received the study vaccines according to protocol procedures.
- Who did not receive a concomitant medication/ product leading to elimination from the PPS (per-protocol) analysis (see Section 6.6.2) up to the 1 month post-Dose 4 visit (Day 391).
- Who did not present an intercurrent medical condition leading to elimination from the PPS analysis for immunogenicity (see Section 6.7), up to the 1 month post-Dose 4 visit (Day 391).
- Who complied with the blood sample timings as specified in Table 10 and Table 6.
- For whom post-vaccination immunogenicity results are available for at least 1 assay.

Impact on the per protocol set for immunogenicity will be determined on a case by case basis.

10.6. Derived and transformed data

Demography

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

Safety

- For solicited symptoms, missing or unevaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).
- For the unsolicited symptoms and concomitant medications/ products/ vaccinations, all vaccinated subjects will be considered and subjects who miss reporting symptoms/concomitant medications/ products/ vaccinations will be treated as subjects without unsolicited symptoms or concomitant medications/ products/ vaccinations, respectively.

Immunogenicity

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

CMI

- The frequency of CD4+ or CD8+ T-cells producing two or more markers (such as interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), upon *in vitro* stimulation with the antigen (induction condition) is calculated by adding an offset of 0.5 to the number of activated CD4+/CD8+ T cells (numerator) divided by the total number of CD4+/CD8+ T cells involved (denominator).
- The frequency of **antigen-specific** CD4+ or CD8+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines/markers among IFN-γ, IL-2, IL-13, IL-17, TNF-α

and/or CD40L, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines upon *in vitro* stimulation in medium only (background condition). For descriptive statistics purposes, differences less or equal to zero (0) are imputed to 1.

10.7. Analysis of demographics

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

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

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

Withdrawal status will be summarised by group using descriptive statistics:

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

No inferential analyses of demographic data are planned.

10.8. Analysis of safety

The analysis for safety will be performed on the ES.

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

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

The same tabulation will be performed for Grade 3 AEs.

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

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

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

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

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

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

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

10.9. Analysis of immunogenicity

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

10.9.1. Within groups assessment

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

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

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

The GMC ratios will be computed for each timepoint by using an ANCOVA model on the logarithm base10 transformation of the concentrations. This model will include the study group, country, age category (40 - 59 years or 60 - 80 years) and smoking status (current or former smokers) as factors and pre-Dose 1 concentration (as covariate).

The difference in terms of seropositivity rate at each timepoint will be also evaluated, presenting point estimate and the 95% CIs at each time point.

10.9.2. Cell-mediated immune response

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

10.10. Interpretation of analyses

All safety and immunogenicity analyses are planned with the intention to estimate the safety and immune response after a third injection. No comparisons are planned for this study and if comparative analyses will be performed they will be done with alpha level of 5% without alpha adjustment.

10.11. 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.

10.11.1. Sequence of analyses

- The analyses will be performed stepwise:
  - A final analysis of the primary epoch including all data from the two vaccination schedules up to and including Day 541 (Visit 9) will be performed in a first step.

  A complete clinical study report, containing all data of the primary epoch will be written and made available to the investigators at this stage.

  - Analyses conducted on the data collected during the follow- up epoch up to and including Day 721 (Visit 10) will be performed in a second step.

  An integrated clinical study report containing all data and analyses of the primary and follow-up epoch will be written and made available to the investigators.

10.11.2. Statistical considerations for interim analyses

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

11. ADMINISTRATIVE MATTERS

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

11.1. Electronic Case Report Form instructions

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

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

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

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

11.2. Study Monitoring by GSK Biologicals

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

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

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

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

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

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

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

11.3. Record retention

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

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

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

11.4. 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.

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

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

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

As per EU regulation, summaries of the results of GSK interventional studies (phase 1-4) in adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

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

11.6. 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.

11.7. Data Sharing

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

12. COUNTRY SPECIFIC REQUIREMENTS

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

For this NTHI MCAT-008 study, there is no intention to conduct specific analyses investigating the relationship between gender and the safety and efficacy of the investigational NTHi-Mcat vaccine. Recruitment will include males and females. To not expose pregnant women and their foetuses/children to an early-phase investigational vaccine, females enrolled in this trial will either be of non-childbearing potential (i.e., have a current tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or be premenarchal or postmenopausal), or if she is of childbearing potential, she must practice adequate contraception for 30 days prior to the beginning of the administration of study treatment, have a negative pregnancy test and continue such precautions during the entire study treatment period and for 2 months after completion of the injection series (Refer to the study protocol, Section 4.2 “Inclusion criteria” and Section 4.3 “Exclusion criteria”). The recruitment will be closed to females who are pregnant or lactating. Similarly, patients becoming or deciding to become pregnant during the study must stop the study treatment administrations.

The indication of the vaccine under investigation is to reduce the frequency of moderate and severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) in patients with a previous history of moderate or severe AECOPD. Historically, COPD was considered a disease of males. The past few decades have seen a shift in this paradigm. In the United States, between the periods of the First National Health and Nutrition Examination Survey (NHANES I) and NHANES III, the prevalence of spirometrically determined moderate COPD increased in women from 50.8 per 1000 to 58.2 per 1000, whereas the prevalence decreased in men from 108.1 per 1000 to 74.3 per 1000.3 Data from the National Health Interview Survey show that the self-reported prevalence of COPD in the United States was stable from 1998 through 2009 and has remained higher in women than in men. A similar trend is seen in other developed countries such as Canada, the Netherlands, and Australia [Aryal, 2013]. There are no reports of gender differences in the efficacy or safety outcomes for patients receiving the investigational NTHi-Mcat vaccine.

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14. APPENDICES

APPENDIX A LABORATORY ASSAYS

Humoral immunity

Serological assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described below and in Table 8. The cut-off and unit of these assays might be subject to change during the course of the study (e.g. in case of assay re-optimization, qualification, (re)validation or standardization). In this case, this will be documented in the clinical study report.

Anti-PD antibodies

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

Anti-PE antibodies

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

Anti-PilA antibodies

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

Anti-UspA2 antibodies

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

Cell-mediated immunity

CMI assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described in Table 9.

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/markers (such as IL-2, IL-13, IL-17, IFN-γ, TNF-α and CD40L) or selected combination of cytokines will be evaluated by flow cytometry.

APPENDIX B CLINICAL LABORATORIES

Table 21 GSK Biologicals' laboratories

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

Table 22 Outsourced laboratories

Laboratory	Address
CEVAC - University of Gent	De Pintelaan, 185 Gent, Belgium

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	207759 (NTHI MCAT-008)
IND number	16531
EudraCT number	2017-002941-31
Amendment number:	Amendment 1
Amendment date:	24 July 2018
Co-ordinating author:	PPD, XPE Pharma & Science for GSK Biologicals

Rationale/background for changes:

- The Medical Dictionary for Regulatory Activities (MedDRA) list with potential immune mediated diseases (pIMDs) has been recently updated with the addition of "gout" as musculoskeletal disorder of interest (including re-arrangement of some other diseases). The main reason for updating the pIMD list in the protocol is so that the investigator can appropriately follow Section 6.5 Contraindications to subsequent vaccination (Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 8.1.5.1 for the definition of pIMDs).
- Table 6 - Interval between study visits, reports the "allowed interval" in the third column. Some of the intervals are marked with the superscript "1" indicating that "subjects will not be eligible for inclusion in the Per-Protocol Set (PPS) for analysis of immunogenicity if the study visit is performed outside of this interval" but not all are marked correctly. Therefore, Table 6 is currently amended to make sure that all the appropriate intervals are marked with the superscript in alignment with the definition of the PPS for analysis of immunogenicity (i.e., subjects will be excluded if not compliant with either the vaccination schedule or the blood sample timings).
- The list of contributors was updated.

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

Cover page

Contributing authors

- PPD *(*Study Delivery Leads)
- PPD (Study Statistician***s***)
- PPD (Lead Statistician***s***)
- PPD (Senior Clinical Research & Development Lead) ***and*** PPD ***(Clinical Research & Development Lead)***
- PPD (Regulatory Affairs Representative***s***)

Table 6 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Visit 1 → Phone contact 1	7 days	7 - 9 days
Visit 1 → Visit 2	30 days	30 - 45 days 1
Visit 1 → Visit 3	60 days	60 - 75 days1
Visit 3 → Phone contact 2	7 days	7 - 9 days
Visit 3 → Visit 4	30 days	30 - 45 days 1
Visit 3 → Visit 5	120 days	120 - 150 days1
Visit 5 → Phone contact 3	7 days	7 - 9 days
Visit 5 → Visit 6	30 days	30 - 45 days 1
Visit 5 → Visit 7	180 days	180 – 210 days1
Visit 7 → Phone contact 4	7 days	7 – 9 days
Visit 7 → Visit 8	30 days	30 – 45 days 1
Visit 7 → Visit 9	180 days	180 – 210 days1
Visit 7 → Visit 10	360 days	360 – 390 days1

[1] Subjects will not be eligible for inclusion in the per-protocol set (PPS) for analysis of immunogenicity if the study visit is performed outside this interval.

8.1.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 15. ***In case of further updates to the pIMDs list, the investigators will be notified in a written communication.***

Table 15 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)

Vasculitides	Blood disorders	Others
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

~~Liver disorders~~	~~Gastrointestinal disorders~~	~~Endocrine disorders~~
• ~~Autoimmune hepatitis~~ • ~~Primary biliary cirrhosis~~ • ~~Primary sclerosing cholangitis~~ • ~~Autoimmune cholangitis~~	• ~~Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis~~ • ~~Celiac disease~~ • ~~Autoimmune pancreatitis~~	• ~~Autoimmune thyroiditis (including Hashimoto thyroiditis)~~ • ~~Grave's or Basedow's disease~~ • ~~Diabetes mellitus type I~~ • ~~Addison's disease~~ • ~~Polyglandular autoimmune syndrome~~ • ~~Autoimmune hypophysitis~~
Neuroinflammatory disorders	***Musculoskeletal disorders***	***Skin disorders***
• ***Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy).*** • ***Optic neuritis.*** • ***Multiple sclerosis.*** • ***Transverse myelitis.*** • ***Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.*** • ***Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.*** • ***Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.*** • ***Demyelinating peripheral neuropathies including:*** - ***Chronic inflammatory demyelinating polyneuropathy,*** - ***Multifocal motor neuropathy*** - ***Polyneuropathies associated with monoclonal gammopathy.*** • ***Narcolepsy.***	• ***Systemic lupus erythematosus and associated conditions*** • ***Systemic scleroderma (Systemic sclerosis), including:*** - ***Diffuse Scleroderma*** - ***CREST syndrome*** • ***Idiopathic inflammatory myopathies, including:*** - ***Dermatomyositis*** - ***Polymyositis*** • ***Anti-synthetase syndrome.*** • ***Rheumatoid Arthritis and associated conditions including:*** - ***Juvenile Idiopathic Arthritis*** - ***Still's disease.*** • ***Polymyalgia rheumatica.*** • ***Spondyloarthropathies, including:*** - ***Ankylosing Spondylitis,*** - ***Reactive Arthritis (Reiter's Syndrome),*** - ***Undifferentiated Spondyloarthritis,*** - ***Psoriatic Arthritis,*** - ***Enteropathic arthritis.*** • ***Relapsing Polychondritis.*** • ***Mixed Connective Tissue disorder.*** • ***Gout.***	• ***Psoriasis.*** • ***Vitiligo.*** • ***Erythema nodosum.*** • ***Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis).*** • ***Lichen planus.*** • ***Sweet's syndrome.*** • ***Localised Scleroderma (Morphoea).***

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

10.5.3. Per-protocol set for analysis of immunogenicity

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

- Who complied with the vaccination schedule, as specified in Table 12 ***and Table 6***.
- Who complied with the blood sample timings as specified in Table 10 ***and Table 6***.

GlaxoSmithKline Biologicals SA

Vaccines R &D

Protocol Amendment 2

eTrack study number and Abbreviated Title	207759 (NTHI MCAT-008)
IND number	16531
EudraCT number	2017-002941-31
Amendment number:	Amendment 2
Amendment date:	24 July 2019
Co-ordinating author:	PPD, GSK Biologicals

Rationale/background for changes:

- The coordinating and contributing authors (page 2) were updated to reflect the current team in this Amendment 2.
- In *Table 8 - Humoral Immunity (Antibody determination)* (section 5.7.3 Laboratory Assays - Humoral antibody responses, page 51) and in *Humoral immunity* subsection (Appendix A - Laboratory Assays, page 94), the new ELISA cut-offs were updated, as result of a recent assay qualification.
- Some typos in the temperature scale reported in the protocol *Assessment of intensity* part (section 8.3.3.2.1, page 69) were corrected.
- A new outsourced Laboratory (CEVAC) was identified for Cell Mediated Immunity (CMI) testing and this new Laboratory was added in the study protocol in *Table 22 - Outsourced laboratories* (Appendix B - Clinical Laboratories, page 95).
- The CMI testing limited to the CD8 measurement was downgraded from secondary to tertiary endpoint (*Secondary* and *Tertiary objectives* and *endpoints*, Synopsis, pages 9 and 13; *Secondary* and *Tertiary objectives*, sections 2.2 and 2.3 respectively, page 34; *Secondary* and *Tertiary endpoints*, sections 10.2 and 10.3 respectively, pages 79 and 80; *Secondary objectives - CMI immunogenicity after third dose*, section 10.4, page 82) because:
  - Alignment of endpoints with other COPD ongoing trials.
  - The assay for CD8+ T cells detection is currently not qualified and there is no plan to qualify it.
- Clarification of the wording in section 10.6, *Derived and transformed data* – CMI (page 84).

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

Cover page

- PPD (Study Statisticians)
- PPD ***(Science Writer)***
- PPD (CLS Study Managers)
- PPD (TCS for GSK Biologicals) and PPD ***(ICON for GSK Biological)*** (Study Data Managers)

5.7.3 Laboratory assays

Humoral antibody responses

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

Table 8 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit*	Cut-off*	Laboratory
SERUM	anti-PilA antibody	ELISA	In house	EU/ml	~~7~~ ***8***	GSK Biologicals** or GSK designated laboratory
	anti-PE antibody				~~8~~ ***16***	
	anti-PD antibody				153	
	anti-UspA2 IgG antibody				~~18~~ ***28***	

EU/mL = ELISA unit per millilitre

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

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

8.3.3.2.1 Assessment of intensity

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

0: < 37.5°C
1: 37.5°C to ***37.9***~~38.0~~°C
2: ***38.0***~~38.1~~°C to ***38.9***~~39.0~~°C
3: ~~>~~≥39.0°C

Synopsis - objectives

Secondary

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

Tertiary

- ***To evaluate the cellular immunogenicity (CD8+ T cell response) of the NTHi-Mcat investigational vaccine.***

Synopsis – endpoints

Secondary

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

Tertiary

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

2 OBJECTIVES

2.2 Secondary objectives

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

2.3 Tertiary objectives

- ***To evaluate the cellular immunogenicity (CD8+ T cell response) of the NTHi-Mcat investigational vaccine.***

10 STATISTICAL METHODS

10.2 Secondary endpoints

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

10.3 Tertiary endpoints

CMI:

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

10.4 Determination of sample size

Secondary objectives:

CMI immunogenicity after third dose

CMI will be evaluated as frequency of CD4+ T-cells ~~and CD8+ T-cells~~ expressing at least two of different ***markers,*** ~~cytokines, and expressing at least one cytokine~~ when stimulated by each antigen PD, PE, PilA and UspA2.

10.6 Derived and transformed data

CMI:

The frequency of **antigen-specific** CD4+ or CD8+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines***/markers*** among IFN-γ, IL-2, IL-13, IL-17, TNF-α and/or CD40L, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ or CD8+ T-cells producing at least 2 cytokines upon *in vitro* stimulation in medium only (background condition).

APPENDIX A LABORATORY ASSAYS

Humoral immunity

Serological assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described below and in Table 8. The cut-off and unit of these assays might be subject to change during the course of the study (e.g. in case of assay re-optimization, qualification, (re)validation or standardization). In this case, this will be documented in the clinical study report.

Anti-PD antibodies

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

Anti-PE antibodies

Anti-PE antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PE antibodies will be determined, using in-house made reference serum. The technical cut-off of the assay is ~~8~~***16*** EU/mL.

Anti-PilA antibodies

Anti-PilA antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PilA antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~7~~***8*** EU/mL.

Anti-UspA2 antibodies

Anti-UspA2 antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-UspA2 antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~18~~***28*** EU/mL.

Cell-mediated immunity

After PBMC stimulation with the relevant antigens, the frequency of $CD4^+$ and/or $CD8^+$ T-cells expressing selected set of cytokines***/markers*** (such as IL-2, IL-13, IL-17, IFN-γ, TNF-α and CD40L) or selected combination of cytokines will be evaluated by flow cytometry.

APPENDIX B CLINICAL LABORATORIES

Table 22 Outsourced laboratories

Laboratory	***Address***
CEVAC - University of Gent	***De Pintelaan, 185 Gent, Belgium***

GlaxoSmithKline Biologicals SA

Vaccines R &D

Protocol Amendment 3

eTrack study number and Abbreviated Title	207759 (NTHI MCAT-008)
IND number	16531
EudraCT number	2017-002941-31
Amendment number:	Amendment 3
Amendment date:	26 May 2020
Co-ordinating author:	PPD, GSK Biologicals

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the conduct or management of the trial.

- **Rationale/background for changes:**
- This protocol amendment 3 outlines measures that may be applicable during special circumstances (e.g. COVID-19 pandemic). The purpose of the amendment is to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity.

However, if the study specific visit and procedures can be completed, then they should be completed according to the protocol, taking into account clinical judgment and local public health guidance to protect the safety of staff and subjects.

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

Cover page:

PPD ***(Science Writer)***

Contributing authors - PPD ~~(Senior Clinical Research & Development Lead) and~~ PPD (Clinical Research & Development Lead)

- PPD (Study Statistician)
- PPD (Lead Statistician)
- ~~PPD (Science Writer)~~
- ~~PPD~~ (Study Delivery Lead)
- ~~PPD~~ (CLS Study Manager)

- PPD (Clinical Safety Representatives)
- PPD ~~(TCS for GSK Biologicals) and~~ PPD (ICON for GSK Biological) (Study Data Manager)
- PPD (Regulatory Affairs Representative)

Synopsis and Section 3:

- Sampling schedule:
  - **Blood samples for assessment of humoral immunogenicity** will be collected from all subjects at Visit 1 (Day 1), Visit 4 (Day 91), Visit 5 (Day 181), Visit 6 (Day 211), Visit 7 (Day 361), Visit 8 (Day 391), Visit 9 (Day 541) and Visit 10 (Day 721)*.

Refer to Section 5.6.18 for study procedures to be considered during special circumstances.

List of abbreviations:

COVID-19	***Coronavirus Disease 2019***

Section 5.5 Outline of study procedures:

Table 5: List of study procedures

Epoch	*Epoch 001*													*Epoch 002*
Type of contact	**Visit 1**	**Phone contact 1**	**Visit 2**	**Visit 3**	**Phone contact 2**	**Visit 4**	**Visit 5**	**Phone contact 3**	**Visit 6**	**Visit 7**	**Phone contact 4**	**Visit 8**	**Visit 9**	**Visit 10** [i]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**	**Day 181**	**Day 188**	**Day 211**	**Day 361**	**Day 368**	**Day 391**	**Day 541**	**Day 721** [h]
Sampling timepoints	**Pre-Vacc I**					**Post-Vacc II**	**Pre-Vacc III**		**Post-Vacc III**	**Pre-Vacc IV**		**Post-Vacc IV**	**Post-Vacc IV**	**Post-Vacc IV**
Blood sampling for antibody determination (~20 ml)	● [f]					●	● [f]		●	● [f]		●	●	● [h]
Record any intercurrent medical conditions [e g]		●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of AEs [e g]		●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of SAEs [e g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of pIMDs [e g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●

[g]. If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs or SAEs (refer to Section 8.1 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 16

[h]. The timepoints for Visit 10 and for blood sampling may change according to extended intervals. Refer to Section 5.6.18 for study procedures to be considered during special circumstances and Table 6 for details on visit intervals

[i] Visit 10 may be a telephone contact during special circumstances. Refer to Section 5.6.18 for study procedures to be considered during special circumstances.

Table 6: Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Visit 7 → Visit 10	360 days	360 – 390 days ***(+120 days under special circumstances)***[1 ^]

^ Refer to Section 5.6.18 for study procedures to be considered during special circumstances. Impact on the per protocol set for immunogenicity will be determined on a case by case basis

Section 5.6.14.1 Blood sampling for immune response assessments

Blood samples for humoral immunogenicity

A volume of approximately 20 mL of whole blood should be drawn from all subjects for each analysis of humoral immune response at each pre-defined timepoint (Visit 1, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9 and Visit 10)*****. After whole blood processing into serum, serum samples should be kept at ≤–20°C until shipment. Refer to the SPM and Central Laboratory manual for more details on sample storage conditions.

**** Refer to Section 5.6.18 for study procedures to be considered during special circumstances.***

Section 5.6.17 Recording of AEs, SAEs, pregnancies and pIMDs

For Epoch 002, this includes the assessment of COVID-19 cases in accordance with the WHO definition. Refer to Section 5.6.18 and 8.3.1 for details.

Section 5.6.18 Study procedures during special circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants (still participating in the study) for Visit 10:

- ***If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 6), then the interval may be extended up to a maximum length of 120 days (i.e. allowed interval for Visit 10 = 360 to 390 days +120 days under special circumstances).***
- ***In case, a physical visit to the clinic is not possible in any circumstances even with the extended interval, safety follow-up may be made by a telephone call or other means of virtual contact, if appropriate. The telephone call/ mode of virtual contact will be considered equivalent to study conclusion visit.***

Section 5.7.2 Biological samples

Sample type	Quantity	Unit	Timepoint	Sub-cohort
Blood for humoral immunogenicity	~20	ml	• Visit 1 (Day 1) • Visit 4 (Day 91) • Visit 5 (Day 181) • Visit 6 (Day 211) • Visit 7 (Day 361) • Visit 8 (Day 391) • Visit 9 (Day 541) • Visit 10 (Day 721)**	All enrolled subjects

***** Refer to Section 5.6.18 for study procedures to be considered during special circumstances and Table 6 for details on extended visit interval.***

Section 5.7.4.1 Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component
Type of contact and timepoint	Sampling timepoint			
~~Day 9~~ ***Visit 9*** (Day 541)	Post-Vacc IV	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
~~Day 10~~ ***Visit 10*** (Day 721)**	Post-Vacc IV	All subjects	~200	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2

Refer to Section 5.6.18 for study procedures to be considered during special circumstances and Table 6 for details on extended visit interval

Section 8.3.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

For Epoch 002, this includes the assessment of COVID-19 cases in accordance with the WHO definition. Cases should be categorised as AEs (unsolicited or AEs leading to withdrawal) or SAEs (refer to Section 8.1 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 16.

Event	Visit 1 Dose 1	6 d post Dose 1	29 d post Dose 1	Visit 3 Dose 2	6 d post Dose 2	29 d post Dose 2	Visit 5 Dose 3	6 d post Dose 3	29 d post Dose 3	Visit 7 Dose 4	6 d post Dose 4	29 d post Dose 4	Study conclusion
Timepoint	Day 1	Day 7	Day 30	Day 61	Day 67	Day 90	Day 181	Day 187	Day 210	Day 361	Day 367	Day 390	Day 721
AEs/SAEs leading to withdrawal from the study**													
SAEs **													
Intercurrent medical conditions leading to exclusion per protocol **													

*** During Epoch 002, if a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as (S)AEs leading to withdrawal) or SAEs (refer to Section 8.1 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the defined time period*

Section 10.5.3 Per-protocol set for analysis of immunogenicity

Impact on the per protocol set for immunogenicity will be determined on a case by case basis.