CONFIDENTIAL

204913 (NTHI-MCAT-006 EXT:001)
Protocol Amendment 1 Final

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

Primary Study vaccine(s) and number(s)	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): • GSK3277513A (10 µg of PD, 10 µg of PE-PilA and 10 µg of UspA2/ AS01E) • GSK3339036A (10µg of PD, 10 µg of PE-PilA, and 3.3µg of UspA2/ AS01E)
Other Study vaccine	• Control: saline Placebo
eTrack study number and Abbreviated Title	204913 (NTHI-MCAT-006 EXT:001)
Investigational New Drug (IND) number	16531
EudraCT number	2016-004248-13
Date of protocol	Final : 10 February 2017
Date of protocol amendment	Amendment 1 Final: 28 June 2018
Title	A long-term follow-up study of the investigational GSK Biologicals' GSK3277511A vaccine in adults.
Detailed Title	A phase 1, multicentre, long term follow-up study up to 4 years after study vaccination to assess immunogenicity and safety of the investigational GSK Biologicals' GSK3277511A vaccine in adults.
Co-ordinating author(s)	PPD (XPE Pharma & Science for GSK Biologicals)
Contributing authors	• PPD (Clinical Epidemiology Project Lead) • PPD ***and*** PPD (Clinical Research & Development Lead***s***) (**Amended 28 June 2018**)

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Contributing authors (continued)	• PPD (Lead Statistician) • PPD ***(Study Statistician)*** **(Amended 28 June 2018)** • PPD, PPD ***and*** PPD PPD (Study Delivery Lead***s***) (**Amended 28 June 2018**) • PPD (CLS Clinical Read-out Team Leader) • PPD ***and*** PPD (CLS Study manager***s***) (**Amended 28 June 2018**) • PPD (Clinical Safety representative) • PPD (Oversight Data Manager) • PPD ***and*** PPD (Study Data Manager***s***) (**Amended 28 June 2018**) • PPD ***and*** PPD (Regulatory Affairs Representative***s***) (**Amended 28 June 2018**)

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204913 (NTHI-MCAT-006 EXT:001)
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Sponsor signatory	Ashwani Kumar Arora Clinical and Epidemiology Research & Development Project Lead, Clinical RDC Italy
Signature	_____
Date	_____

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Protocol Amendment 1 Rationale

Amendment number: Amendment 1

Rationale/background for changes:

- Table 3 of the protocol (Intervals between study visits) was updated as follow:

  - Optimal length of interval and allowed intervals were updated to avoid the risk of accumulating up to five shortest or longest allowed intervals with possible anticipation/delay of subject's last visit +/– 100 days from the optimal length of the study.

  - Footnote 1 was added to Table 3 to specify that the indication of the month of the visit (i.e. Visit 1 [Month 20]) in the Interval column is an approximate period (label) and not an exact requirement to plan the visit during a specific study month.

  - Footnote 2 was added to Table 3 to define how to count a calendar month for planning the visits.

- The definition of "calendar month" was added to the Glossary of terms.
- The protocol was aligned with the Statistical Analysis Plan Amendment, regarding the model used for the immunogenicity analysis.
- Table 5 and the laboratory assays appendix were updated with new cut-off values, since new optimized assays have been developed during the study. As the ANCOVA model used for the statistical analysis will include the group category as fixed effects and the pre-Dose 1 concentration in NTHi-Mcat-001 study as regressor, it is to be noted that pre-Dose 1 antibody concentrations in NTHi-Mcat-001 study were reported using the first generation ELISA with a cut-off of 7 EL.U/mL. However, the 2 assay versions have been shown to be technically aligned, allowing the exploratory comparison of anti-PilA ELISA data between NTHi-Mcat-001 and NTHi-Mcat-006 studies.
- The list of contributors was updated.
- Minor edits have been made in alignment with the GSK protocol template.

Protocol Amendment 1 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(s) 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(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

eTrack study number and Abbreviated Title	204913 (NTHI-MCAT-006 EXT:001)
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Investigator name _____

Signature _____

Date _____

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Sponsor Information

1. Sponsor

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

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

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

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.2.

SYNOPSIS

Detailed Title	A phase 1, multicentre, long term follow-up study up to 4 years after study vaccination to assess immunogenicity and safety of the investigational GSK Biologicals' GSK3277511A vaccine in adults.
Indication	Active immunisation for the reduction of frequency of moderate and severe acute exacerbations of COPD in patients with previous history of COPD.
Rationale for the study and study design	• **Rationale for the study**: The purpose of this long-term follow-up of a Phase I study is to evaluate the kinetics of the antibody response to NTHi-Mcat antigens and long-term safety, in subjects aged between 50–71 years at the time of enrolment in the NTHi-Mcat-001 study, and who were having a significant smoking history (≥ 10 pack-years). These subjects were previously exposed to two adjuvanted formulations of the NTHi-Mcat vaccine administered according to a 0, 2 months schedule in the NTHi-Mcat-001 (201281) study. The subjects that had received saline placebo controls will also be included in this follow-up study to make comparisons with the investigational vaccines. No vaccinations will be administered in this trial. • **Rationale for the study design**: Only the subjects included in STEP 2 of the primary vaccination study (NTHi-Mcat-001/ 201281) will be enrolled in this follow-up study. These study groups were chosen because the subjects included reflect the primary age range (50-71 years old at the time of enrolment in the NTHi-Mcat-001 study) of the target population (COPD patients with a previous history of exacerbation). STEP 2 of the NTHi-Mcat-001 study included 90 healthy adults, 50–71 years old at the time of enrolment, with a smoking history of at least 10 pack-years, either receiving placebo control, or one of two AS01E adjuvanted formulations, i.e. 10 µg of PD, 10 µg of PE-PilA and 10 µg of UspA2 (Group 10-10-10-AS) or 10 µg of PD, 10 µg of PE-PilA and 3.3 µg of UspA2 (Group 10-10-3-AS) (30/group).
Objective(s)	**Primary** • To assess the persistence of humoral antibodies up to 3 years after the last planned visit (Month 14) in the NTHi-Mcat-001 study.

Secondary

- To assess the safety of the investigational NTHi-Mcat vaccine in terms of serious adverse events and potential immune-mediated diseases up to 3 years after the last planned visit (Month 14) in the NTHi-Mcat-001 study.

Study design

- Experimental design: Phase I , controlled, multi-centric, single-country, long term follow-up study with three parallel groups from the NTHi-Mcat-001 study.
- Duration of the study: For each subject, the study will last approximately 30 months.
- Epoch 001: Long-term follow-up starting at Visit 1 (Month 20) and ending at Visit 6 (Month 50).
- Primary completion Date (PCD): Visit 6 (Month 50).
- End of Study (EoS): Last testing results released of samples collected at Visit 6, will be achieved no later than 8 months after last subject last visit (LSLV).
- Study groups of the NTHi-Mcat-001 study:
  - 10-10-10-AS: Up to 30 subjects who have received two doses of the AS01E-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine during STEP 2 of NTHi-Mcat-001 study containing 10µg of PD, PE-PilA and UspA2.
  - 10-10-3-AS: Up to 30 subjects who have received two doses of the AS01E-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine during STEP 2 of NTHi-Mcat-001 study containing 10µg of PD, 10µg of PE-PilA, and 3.3µg of UspA2.
  - PLACE2: Up to 30 subjects who have received two doses of placebo (saline solution) during STEP 2 of the NTHi-Mcat-001 study.

Synopsis Table 1 Study groups and epochs foreseen in the study

Study Groups*	Number of subjects	Epoch
		Epoch 001
10-10-10-AS	up to 30	x
10-10-3-AS	up to 30	x
PLACE2	up to 30	x

*Study groups of NTHi-Mcat-001 study. No vaccinations will be administered in this trial.

- Control: placebo control

Blinding: open. This is a long-term follow-up study following up on the observer blinded NTHi-Mcat-001. Data from the NTHi-Mcat-001 study may still be blinded at the start of this study; therefore, at the time of enrolment, subjects may not be aware of the study group to which they were assigned in the NTHi-Mcat-001 study.

- Sampling schedule: Blood samples for humoral immunogenicity will be collected from all subjects at Visit 1 (Month 20), Visit 2 (Month 26), Visit 3 (Month 32), Visit 4 (Month 38), Visit 5 (Month 44) and Visit 6 (Month 50).
- Type of study: extension of other protocol(s) (NTHi-Mcat-001 [201281]).
- Data collection: Electronic Case Report Form (eCRF)
- Safety monitoring: Follow-up of Serious Adverse Events (SAEs) and potential immune-mediated diseases (pIMDs). Refer to Section 8.4 for detailed description of safety monitoring.

Number of subjects

Up to 90 subjects who were exposed in STEP 2 of study NTHi-Mcat-001 (204913) and who agree to participate in the present study will be enrolled at the same study centres in Belgium.

Endpoint(s)

Primary

- Humoral immune response to the components of the NTHi Mcat investigational vaccine formulations at Month 20, Month 26, Month 32, Month 38, Month 44 and Month 50 in all subjects:
  - Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations.

Secondary

- Occurrence of any serious AE (SAE), during the entire study period in all subjects.
- Occurrence of any potential immune-mediated disease (pIMD) during the entire study period in all subjects.

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LIST OF ABBREVIATIONS

ANCOVA	analysis of ***co***variance (**Amended 28 June 2018**)
AE	adverse event
AECOPD	acute exacerbation of COPD
Al	aluminium
AS	adjuvant system
COPD	chronic obstructive pulmonary disease
CRDL	Clinical Research & Development Lead
CSR	clinical study report
eCRF	electronic Case Report Form
ELISA	enzyme-linked immunosorbent assay
EU/mL	ELISA unit per millilitre
EMA	European Medicines Agency
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
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
IEC	Independent Ethics Committee
Ig	immunoglobulin
IRB	Institutional Review Board
LAR	legally acceptable representative

Mcat	*Moraxella catarrhalis*
NTHi	non-typeable *Haemophilus influenzae*
PD	protein D
PE	protein E
PilA	type IV pili subunit
pIMD	potential immune-mediated disease
SAE	serious adverse event
SDV	source document verification
SPM	Study Procedures Manual
TVC	total vaccinated cohort
UspA2	ubiquitous surface protein A2 of *Moraxella catarrhalis*
WHO	World Health Organisation
µL	microliter

GLOSSARY OF TERMS

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 open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not. 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). In a double blind study, the subject, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and the review or analysis of data are all unaware of the treatment assignment. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group.

Calendar month **(Amended 28 June 2018)**	***A period from a specified day in one month to the day numerically corresponding to that day in the following month independently on the specific length of the month (i.e. from the 5th of February to the 5th of March)***
Current smoker:	A person who is currently smoking or who has stopped smoking within the past 6 months.
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 6.1.2 and 10.4 for details on criteria for evaluability).
Former smoker:	A person who stopped smoking for at least 6 months.
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.

Intercurrent medical conditions:	Medical conditions that, by potentially altering the immune response of a subject (except pregnancies), may lead to a subject being eliminated from analysis.
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.
Legally acceptable representative **(The terms legal representative or legally authorized representative are used in some settings.):**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Pack-years of smoking:	Pack-years is a quantification of cigarette smoking, a way to measure the total amount a person has smoked in the course of his/ her lifetime. The number of pack-years is calculated as follows: (average number of *cigarettes* smoked per day x number of years smoked)/ 20 E.g. a smoking history of 10 pack-years means having smoked 20 cigarettes per day for 10 years, or having smoked 10 cigarettes per day for 20 years. *Note*: For the purpose of this study, pipe and/or cigar use should not be used to calculate pack-year history.
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
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(s)/product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

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

The prevalence of COPD is increasing. Using epidemiological models, about 227.3 million COPD cases are estimated to have occurred in the year 1990 among people aged 30 years or more, corresponding to a global prevalence of 10.7% (95% confidence interval (CI) 7.3%–14.0%) in this age group. The number of COPD cases increased to 384 million in 2010, with a global prevalence of 11.7% (8.4%–15.0%) [Adeloye, 2015]. In the United States (US), over 2.7 million adults were estimated to have COPD in 2011, with about 135 000 deaths reported [CDC, 2012]. In 2010, the US government spent nearly US$ 49.9 billion on COPD, including 29.5 billion spent on direct health care, 8.0 billion on indirect morbidity and 12.4 billion on indirect mortality costs, respectively [CDC, 2012]. 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]. The rate at which acute exacerbations occur varies greatly between patients, with severe patients exacerbating more often. 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]. In COPD patients, acquisition of new bacterial strains is believed to be an important cause of AECOPD [Sethi, 2002]. Although estimates vary widely, 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-year 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. A meta-analysis of antibiotic use in COPD exacerbations revealed inconsistent effects, with more pronounced positive effects on treatment success in hospitalized patients vs outpatients, but no significant effects on mortality or length of hospital stay [Vollenweider, 2012]. Moreover, 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 further evaluated in this follow-up 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.

PD acts as a glycerophosphodiesterase and is involved in the adhesion and invasion via phosphorylcholine decoration of the bacterial membrane's components. Passive transfer of anti-PD sera induces protection in the NTHi chinchilla otitis media model [Novotny, 2006], and vaccination with PD induces protection in the mouse nasopharyngeal colonisation model [Forsgren, 2008].

During the infection process, PE is involved in the adhesion of the bacteria to human respiratory and mucosal cells and in the resistance to human complement, a key component of the innate immune system. PilA is involved in bacterial biofilm formation and in the adhesion to human cells mechanism. Anti-PilA antibodies were shown to strongly reduce biofilm formation, *in vitro* and *in vivo* in preclinical animal models [Jurcisek, 2007]. It was demonstrated that antibodies against PE and PilA strongly reduce nasopharyngeal colonisation in mice and/or otitis media in a chinchilla model [Ronander, 2009; Jurcisek, 2007; Novotny, 2009; *GSK unpublished data*]. Preclinical experiments demonstrated that even if PE and PilA are expressed as a fusion protein (PE PilA), the biological activities of elicited antibodies against PE and PilA are retained [*GSK unpublished data*].

UspA2 is a putative autotransporter macromolecule and is a vitronectin-binding protein. UspA2 seems to be involved in the ability of Mcat to resist the bactericidal activity of normal human serum [Attia, 2005]. UspA2 has been shown to induce cross-bactericidal antibody production and cross-protection in a mouse lung colonisation model [Chen, 1996].

The target population of GSK NTHi-Mcat vaccine are COPD patients, who are often elderly and 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.

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]01E and AS04C) were already evaluated in two previous Phase 1 clinical trials (NTHi-002 in healthy adults 18-40 years old and NTHi-003 in current and former healthy smokers 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 (i.e. 10 µg) and the adjuvant system (i.e. AS01E) that was used in the primary study of this long-term follow-up assessment.

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

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

The purpose of this long-term follow-up of a Phase I study is to evaluate the kinetics of the antibody response to NTHi-Mcat antigens and long-term safety, in subjects 50–71 years old at the time of enrolment in the NTHi-Mcat-001 study, and who were having a significant smoking history (≥ 10 pack-years). These subjects were previously exposed to two adjuvanted formulations of the NTHi-Mcat vaccine administered according to a 0, 2 months schedule in the NTHi-Mcat-001 (201281) study. No vaccination will be administered in this trial.

The subjects that had received saline placebo controls will also be included in this follow-up study to make comparisons with the investigational vaccines.

The immunogenicity data collected in this long-term follow-up study will provide insight regarding when a booster dose may be required.

Because an adjuvanted formulation was used in the NTHi-Mcat-001 study, we will continue to closely monitor potential immune-mediated diseases in this long-term follow-up study. Serious adverse events (including those related to study participation or concurrent GSK medication/vaccine) will be recorded as per standard process.

1.2.2. Rationale for the study design

Only the subjects included in STEP 2 of the primary vaccination study (NTHi-Mcat-001/ 201281) will be enrolled in this follow-up study. These study groups were chosen because the subjects included reflect the primary age range (50-71 years at the time of enrolment) of the target population (COPD patients with a previous history of exacerbation). STEP 2 of the NTHi-Mcat-001 study included 90 healthy adults, 50–71 years old at the time of enrolment, with a smoking history of at least 10 pack-years, either receiving placebo control, or one of two AS01E adjuvanted formulations, i.e. 10 µg of PD, 10 µg of PE-PilA and 10 µg of UspA2 (Group 10-10-10-AS) or 10 µg of PD, 10 µg of PE-PilA and 3.3 µg of UspA2 (Group 10-10-3-AS) (30/group).

1.3. Benefit: Risk Assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of 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
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.

1.3.2. Benefit Assessment

Benefits considerations include:

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

1.3.3. Overall Benefit: Risk Conclusion

The balance of anticipated benefits and apparent risks associated with this long-term follow-up study are acceptable as there is no administration of NTHi-Mcat vaccine planned in this study and the risks from the study procedures are believed to be acceptable.

2. OBJECTIVE(S)

2.1. Primary objective

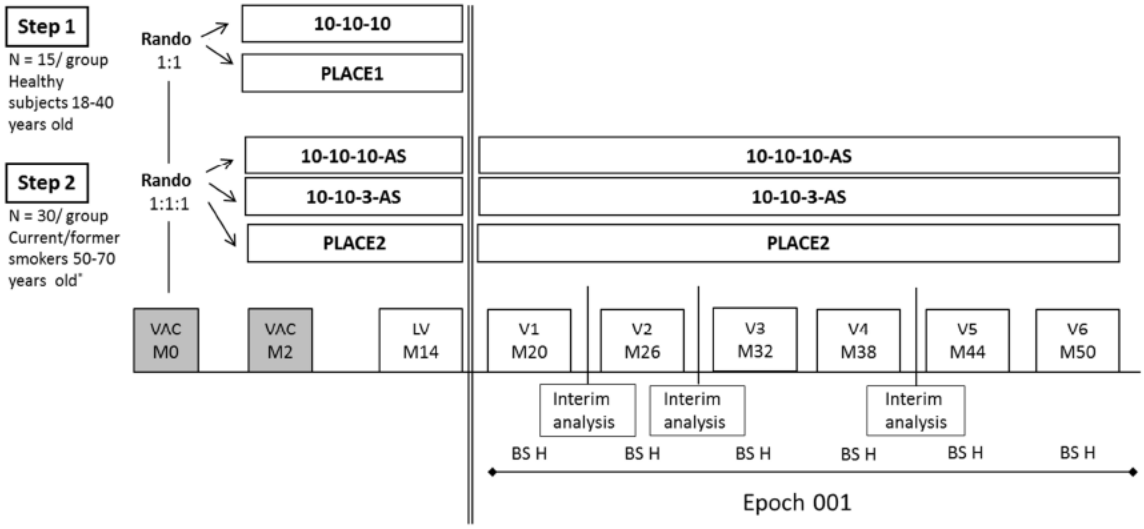
- To assess the persistence of humoral antibodies up to 3 years after the last planned visit (Month 14) in the NTHi-Mcat-001 study.

2.2. Secondary objective

- To assess the safety of the investigational NTHi-Mcat vaccine in terms of serious adverse events and potential immune-mediated diseases up to 3 years after the last planned visit (Month 14) in the NTHi-Mcat-001 study.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design overview



BS H = blood sample for humoral immune responses;
Rando = randomisation; **LV**= Last Visit of NTHi-Mcat-001 study; **V** = Visit of NTHi-Mcat-006 study ; **M** = Month; **VAC** = vaccination (indicated in grey);
* With a cigarette smoking history ≥10 pack-years (calculation pack-years = average number of cigarettes smoked per day x number of years smoked)/20

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 I, controlled, multi-centric, single-country, long term follow-up study with three parallel groups from NTHi-Mcat-001 study.
- Duration of the study: For each subject, the study will last approximately 30 months.
- Epoch 001 : Long-term follow-up starting at Visit 1 (Month 20) and ending at Visit 6 (Month 50).
- Primary completion Date (PCD): last subject of Visit 6 (Month 50).

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released for samples collected at Visit 6.

Refer to glossary of terms for the definition of EoS.

- Study groups of NTHi-Mcat-001 study:
  - **10-10-10-AS:** Up to 30 subjects who have received two doses of the AS01E-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine during STEP 2 of NTHi-Mcat-001 study containing 10µg of PD, PE-PilA and UspA2.
  - **10-10-3-AS** : Up to 30 subjects who have received two doses of the AS01E-adjuvanted GSK Biologicals' NTHi-Mcat investigational vaccine during STEP 2 of NTHi-Mcat-001 study containing 10µg of PD, 10µg of PE-PilA, and 3.3µg of UspA2.
  - **PLACE2** : Up to 30 subjects who have received two doses of placebo (saline solution) during STEP 2 of the NTHi-Mcat-001 study.

Table 1 Study groups and epochs foreseen in the study

Study groups*	Number of subjects	Epoch
		Epoch 001
10-10-10-AS	up to 30	x
10-10-3-AS	up to 30	x
PLACE2	up to 30	x

*Study groups of NTHi-Mcat-001 study. No vaccinations will be administered in this trial.

- **Control**: placebo control.
- **Blinding**: This is a long-term follow-up study following up on the observer blinded NTHi-Mcat-001. Data from the NTHi-Mcat-001 study may still be blinded at the start of this study; therefore, at the time of enrolment, subjects may not be aware of the study group to which they were assigned in the NTHi-Mcat-001 study.
- **Sampling schedule**: Blood samples for humoral immunogenicity will be collected from all subjects at Visit 1 (Month 20), Visit 2 (Month 26), Visit 3 (Month 32), Visit 4 (Month 38), Visit 5 (Month 44) and Visit 6 (Month 50).
- **Type of study**: extension of other protocol(s) (NTHi-Mcat-001 [201281]).
- **Data collection**: Electronic Case Report Form (eCRF)
- **Safety monitoring**: Follow-up of Serious Adverse Events (SAEs) and potential immune-mediated diseases (pIMDs). Refer to Section 8.4 for detailed description of safety monitoring.

4. STUDY COHORT

4.1. Number of subjects/centres

A total of approximately 90 subjects who were exposed in STEP 2 of study NTHi-Mcat-001 (201281) and who agree to participate in the present study will be enrolled at the same study centres in Belgium.

Overview of the recruitment plan:

At the time of the initiation of this long term follow-up study, the investigator will contact all subjects who were enrolled in 10-10-10-AS, 10-10-3-AS and PLACE2 groups of study NTHi-Mcat-001 (201281) at the study centres in Belgium and who received a full vaccination course with the investigational vaccines.. The reason for non-participation in the long-term follow-up study will be documented in the site's screening log.

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 previously participated in STEP 2 of study NTHi-Mcat-001 (201281), and performed the last study visit (Month 14) and received the 2 study vaccinations.
- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. return for follow-up visits). And subjects' Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol.
- Written informed consent obtained from the subject/ LAR(s) of the subject prior to performance of any study specific procedure.

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) during the period starting 30 days before the first follow-up study visit (Month 19 to Month 20), or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since the end of the NTHi-Mcat-001 study. For corticosteroids, this will mean prednisone $\geq$ 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).

- 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).
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first follow-up visit or planned administration during the study period.
- Current alcoholism and/or drug abuse.
- 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.
- 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:

- Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject/LAR(s) informed consent, as appropriate.
- 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 and/or each subject's LAR(s), 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 have been assigned sequentially to the subjects who have consented to participate in the parent trial, according to the range of subject identification numbers allocated to each study centre, but different identification numbers will be used for this follow-up.

5.3. Method of blinding

No vaccine exposure and randomization is overseen in this study, and thus no blinding procedure is in place. However, the laboratory in charge of the immunogenicity testing will be blinded to the treatment subjects received in parent trial, 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 Study Procedures Manual (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

Table 2 List of study procedures

Epoch	Epoch 001					
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Timepoints1	**Month 20**	**Month 26**	**Month 32**	**Month 38**	**Month 44**	**Month 50**
Sampling timepoints	**Follow-up Y1**		**Follow-up Y2**		**Follow-up Y3**	
Informed consent	●					
Check inclusion/exclusion criteria	●					
Collect demographic data	●					
Medical history	●					
Physical examination	●[3]	○[4]	○[4]	○[4]	○[4]	○[4]
Laboratory assays						
Blood sampling for antibody determination and assay validation/development (~20 ml)	●	●	●	●	●	●
Safety assessment						
Record any concomitant medications/vaccinations[2]	●	●	●	●	●	●
Record any intercurrent medical conditions5	●	●	●	●	●	●
Recording of any pIMDs	●	●	●	●	●	●
Recording of SAEs	●	●	●	●	●	●
Study Conclusion						●

Note: The double-line borders following Month 20, Month 26 and Month 38 indicate the analyses which will be performed on all data obtained up to Month 20, Month 26 and Month 38, respectively. The study may be stopped if the stopping guidelines indicated in section 10.9.2 are met.

Y = year; **pIMD** = potential immune mediated diseases; **SAE** = serious adverse events.

● 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.

[1] Timepoints are indicated starting from dose 1 vaccination in NTHi-Mcat-001 study.

[2] Concomitant medication/products/vaccination as indicated in Section 6.1.1 need to be recorded.

[3] Complete physical examination including vital signs (systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest)

[4] Symptom directed physical examination.

[5] Medical conditions that, by potentially altering the immune response of a subject (except pregnancies), may lead to a subject being eliminated from analysis.

The investigator must arrange study visits within the interval provided in Table 3.

Table 3 Intervals between study visits (Amended 28 June 2018)

Interval[1]			Optimal length of interval[2]	Allowed interval
Visit 1 (Month 20)	→	Visit 2 (Month 26)	***6 calendar months after Visit 1 NTHI MCAT 006***	***±20 elapsed days from optimal planned visit day***
Visit ***1*** (Month ***20***)	→	Visit 3 (Month 32)	***12 calendar months after Visit 1 NTHI MCAT 006***	***±20 elapsed days from optimal planned visit day***
Visit ***1*** (Month ***20***)	→	Visit 4 (Month 38)	***18 calendar months after Visit 1 NTHI MCAT 006***	***±20 elapsed days from optimal planned visit day***
Visit ***1*** (Month ***20***)	→	Visit 5 (Month 44)	***24 calendar months after Visit 1 NTHI MCAT 006***	***±20 elapsed days from optimal planned visit day***
Visit ***1*** (Month ***20***)	→	Visit 6 (Month 50)	***30 calendar months after Visit 1 NTHI MCAT 006***	***±20 elapsed days from optimal planned visit day***

[1]The indication of the month of the visit (i.e. Visit 1 (Month 20)) is an approximate period (label) and not an exact requirement to plan the visit during a specific study month.
[2]Refer to glossary of terms for the definition of the calendar month, in order to plan the visits accordingly. In case a visit occurs on day 31st of a month, the following visit should be planned on the 31st of the 6th subsequent month. If not possible (due to the fact that the following visit is to be planned in a month with less than 31 days) the following visit should be planned on the last day of the 6th subsequent month (i.e. Visit 1: 31 August 2017 Visit 2: 28 February 2018).

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject/subject's LAR(s) must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate.

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 subject number from parent trial and 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 retrieving the information already present in the NTHi-Mcat-001 parent study database and interview and record any pre-existing conditions or signs and/or symptoms present in a subject starting from the completion of the NTHi-Mcat-001 parent study until the start of this study (Visit 1) in the eCRF.

5.6.5. Physical examination

Perform a complete physical examination of the subject at Visit 1, including resting vital signs (systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest). Collected information needs to be recorded in the eCRF.

Physical examination at each study visit subsequent to Visit 1 will be performed only if the subject indicates that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

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

5.6.6. 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.

5.6.6.1. Blood sampling for antibody determination and assay validation/development

Blood samples will be taken at each study visit as specified in Section 5.5.

A volume of approximately 20 mL of whole blood should be drawn at each pre-defined time point. After centrifugation, serum samples should be kept at –20°C or below until shipment. Refer to the SPM and to the Central Laboratory Manual for more details on sample storage conditions.

5.6.7. 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 6.1.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.2.

5.6.8. Recording SAEs and pIMDs

- Refer to Section 8.2 for procedures for the investigator to record SAEs and pIMDs. Refer to Section 8.3 for guidelines and how to report SAE and pIMD reports to GSK Biologicals.
- The subjects/subjects' LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.

5.6.9. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness.
- complete study conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

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

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

- 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 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 Belgium 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/subject's LAR(s).

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 by 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 10.4 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 or the 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 in the Central Laboratory Manual.

5.7.2. Biological samples

Table 4 Biological samples (Amended 28 June 2018)

Sample type	Timepoint	Cohort	N° of subjects	Quantity	Unit
Blood for antibody determination and assay development	Visit 1 (Month 20)	All enrolled subjects	up to 90	~20	ml
	Visit 2 (Month 26)	All enrolled subjects	up to 90	~20	ml
	Visit 3 (Month ***32***)	All enrolled subjects	up to 90	~20	ml
	Visit 4 (Month 38)	All enrolled subjects	up to 90	~20	ml
	Visit 5 (Month 44)	All enrolled subjects	up to 90	~20	ml
	Visit 6 (Month 50)	All enrolled subjects	up to 90	~20	ml
Total quantity of blood for each subject				~120	mL

Note: Refer to Table 3 for detailed information on intervals between study visits. **(Amended 28 June 2018)**

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.

Serological assays for the quantification of antibodies will be performed by ELISA at GSK Biologicals' laboratory or a GSK designated laboratory using standardised procedures (refer to Table 5).

Table 5 Humoral Immunity (Antibody determination) (Amended 28 June 2018)

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

ELISA: Enzyme-Linked Immunosorbent Assay; **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 report.
**Refer to APPENDIX B for the laboratory addresses.
***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 components of either the NTHi-Mcat investigational vaccines and/or to other respiratory pathogens. The research may include, but is not limited to:

- Serum bactericidal activity assays
- Anti-PD, -PE, -PilA, UspA2 functional assays

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

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

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

Table 6 Immunological read-outs

Blood sampling time point		No. subjects	Component
Type of contact	Sampling time point		
Visit 1	Month 20	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 2	Month 26	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 3	Month 32	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 4	Month 38	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 5	Month 44	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 6	Month 50	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies

Note: Refer to Table 3 for detailed information on intervals between study visits. **(Amended 28 June 2018)**

5.7.5. Immunological correlates of protection

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

6. STUDY VACCINE AND ADMINISTRATION

Not applicable. No vaccinations will be administered in this trial.

6.1. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator or delegate should question the subject and/or the subject's LAR(s) about any medications/products taken and vaccinations received by the subject.

6.1.1. Recording of concomitant medications/products and concomitant vaccinations

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

- Any concomitant medications/products/vaccines listed in Section 6.1.2.

- 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.

6.1.2. 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 10.4 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) 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 (for adult subjects), or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Immunoglobulins and/or any blood products administered during the study period.

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

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

Subjects may be eliminated from the per-protocol cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (i.e. confirmed immunosuppressive or immunodeficient condition, including HIV).

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 a serious adverse event (SAE) as provided in this protocol.

The safety oversight will be provided by the safety review team through the ongoing routine safety monitoring.

Each subject/subject's LAR(s) will be instructed to contact the investigator immediately should they/the subject 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.
- Significant failure of expected pharmacological or biological action.
- 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).

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. 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 SAE if they meet the definition of a SAE (refer to Sections 8.1.1 and 8.1.2).

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.

8.1.4. Adverse events of specific interest

8.1.4.1. 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 7.

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 7 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

When there is enough evidence to make any of the above diagnoses, the medical condition 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. Detecting and recording serious adverse events

8.2.1. Time period for detecting and recording serious adverse events

The time period for collecting and recording SAEs will begin at the first study visit and will end at study conclusion following last study visit for each subject. See Section 8.3 for instructions on reporting of SAEs.

All SAEs leading to withdrawal from the study will be collected and recorded from the time of the first study visit.

All SAEs related to the study vaccine(s) that occurred since the end of the primary study NTHi-Mcat-001 (201281) will be collected retrospectively, after informed consent is obtained.

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 of pIMDs will begin at the first study visit and will end at study conclusion following the last study visit. See section 8.3.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for SAEs is given in Table 8.

Table 8 Reporting periods for collecting safety information

Event	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Study Conclusion
	Month 20	Month 26	Month32	Month 38	Month 44	Month 50	Month 50
SAEs							
pIMDs							
Intercurrent medical conditions*							

* Medical conditions that, by potentially altering the immune response of a subject (except pregnancies), may lead to a subject being eliminated from analysis.

8.2.2. Post-Study serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE reporting period defined in Table 8. Investigators are not obligated to actively seek 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 vaccine(s) administered in the primary study, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.2.3. Evaluation of serious adverse events

8.2.3.1. Active questioning to detect serious adverse events

As a consistent method of collecting SAEs, the subject or the subject's LAR(s) should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine(s) or since the previous visit?*'

When a 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 a 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 SAE and not the individual signs/symptoms.

8.2.3.2. Assessment of serious adverse events

8.2.3.2.1. Assessment of intensity

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

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities

An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.2.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccine(s) and the occurrence of each SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the SAE 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 SAE 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(s) will be considered and investigated. The investigator will also consult the IB and/or SmPC for marketed products 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.

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.
- Erroneous administration.
- Other cause (specify).

8.2.3.2.3. Assessment of outcomes

The investigator will assess the outcome of all 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. Reporting of serious adverse events

8.3.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 9, once the investigator determines that the event meets the protocol definition of a SAE.

pIMDs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 9, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 9 Timeframes for submitting serious adverse event 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/pIMDs	24 hours*‡	Electronic Expedited Adverse Events Report	24 hours*	Electronic Expedited Adverse Events Report

*Timeframe allowed after receipt or awareness of the information.
‡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/pIMDs.

8.3.2. Contact information for reporting serious adverse events and pIMDs

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

8.3.3. 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.

8.3.3.1. 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.

8.3.4. 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 8.3.3.1 for back-up system in case the electronic reporting system does not work.

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

When additional SAE 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 9.

8.3.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.3.1. 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(s) and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.4. Follow-up of serious adverse events

8.4.1. Follow-up of serious adverse events

8.4.1.1. Follow-up during the study

After the initial 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 9).

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.

8.4.1.2. 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 as applicable.

If the study is concluded, the investigator should send the information via email to safety (Email address: PPD) using SAE paper form.

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 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. Treatment of serious adverse events

Treatment of any SAE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE / pIMD should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.1).

8.6. Subject card

Study subjects/LAR(s) 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/LAR(s). 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/LAR(s) must be instructed to keep subject cards in their possession at all times during the study duration.

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 at least 3 attempts (e.g. 3 telephone calls) 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, by the subject's LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Protocol violation (specify).

- Consent withdrawal, not due to a serious 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 LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of SAEs 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 until resolution of the event (see Section 8.4.1.2).

9.3. Screen and baseline failures

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

The following information will be collected for screening failures:

- Informed consent.
- Inclusion/exclusion criteria.
- Demographic data.
- SAEs related to study participation, to concomitant use of GSK products or any fatal SAEs.
- Screening conclusion.

10. STATISTICAL METHODS

10.1. Primary endpoint

- Humoral immune response to the components of the NTHi Mcat investigational vaccine formulations at Month 20, Month 26, Month 32, Month 38, Month 44 and Month 50 in all subjects:
  - Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations.

10.2. Secondary endpoint(s)

- Occurrence of any serious AE (SAE), during the entire study period in all subjects.
- Occurrence of any potential immune-mediated disease (pIMD) during the entire study period in all subjects.

10.3. Determination of sample size

As this is a follow-up study, no sample size has been computed. All eligible subjects from STEP 2 of the NTHi-Mcat-001 (201281) are planned to be enrolled. Should the enrolled subjects be less than 30 in total, consideration will be given to discontinuation of the study by the Sponsor.

10.4. Cohorts for Analyses

The following subject cohorts will be evaluated.

10.4.1. Total vaccinated cohort

The total vaccinated cohort (TVC) will include all subjects from STEP 2 of NTHi-Mcat-001 (201281) enrolled in this follow-up study:

- A safety analysis based on the TVC will include all subjects enrolled in this follow-up study.
- An immunogenicity analysis based on the TVC will include all subjects for whom immunogenicity data are available.

The TVC analysis will be performed per treatment administered in the parent study NTHi-Mcat-001 (201281).

10.4.2. Per-protocol cohort for analysis of immunogenicity

The per-protocol cohort for immunogenicity will consist of all subjects from the TVC who will comply with eligibility criteria, study procedures up to the last subject last visit and had immunogenicity results in the epoch.

More specifically, the Per-protocol cohort for immunogenicity will include all eligible subjects:

- Who met all eligibility criteria.
- Who did not receive a concomitant medication/ product/vaccine leading to the elimination from the Per-protocol analysis for immunogenicity (see Section 6.1.2).
- Who did not present with an intercurrent medical condition leading to elimination from the Per-protocol analysis for immunogenicity (see Section 6.2).
- Who complied with at least one of the immunogenicity blood sample timings as specified in Table 5.
- For whom immunogenicity results are available for at least one assay in at least one of the follow-up time points.

10.5. Derived and transformed data

- **Immunogenicity**

The technical assay cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.

A seronegative subject is a subject whose titre is below the cut-off value.

A seropositive subject is a subject whose titre is greater than or equal to the cut-off value.

Seroconversion is defined as the appearance of antibodies (i.e. titre greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.

The geometric mean concentrations (GMC) are computed by taking the anti-log of the mean of the log concentration transformations. Values to be used for the antibody concentrations below the assay cut-off will be described in the Statistical Analysis Plan (SAP).

Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

10.6. Analysis of immunogenicity

The primary analysis will be based on the per-protocol cohort for analysis of immunogenicity. If, in any study group, the percentage of enrolled subjects with serological results excluded from the per-protocol cohort for analysis of immunogenicity is 10% or more, a second analysis based on the TVC will be performed to complement the per-protocol analysis.

Three interim analyses will be performed on all data obtained up to Month 20, Month 26 and Month 38, respectively. The study may be stopped if the stopping guidelines indicated in section 10.9.2 are met.

10.6.1. Humoral immune response

Within groups evaluation

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

- Seropositivity rate and the exact 95% CI will be tabulated.
- GMCs and their 95% CI will be calculated.
- Antibody concentrations distribution will be investigated using Reverse Cumulative Curves.
- Subject graphs of immunogenicity results over time will be provided.

Between groups evaluation

Comparative analyses will be exploratory with the aim to characterise the difference between the 10-10-10-AS and 10-10-3-AS groups in humoral immune response.

The difference in terms of GMCs will be evaluated by computing the 95% CIs of the GMC ratio between groups by using a one-way ***ANCOVA*** model on the logarithm10 transformation of the concentrations/ titres. The ***ANCOVA*** model will include the group category as fixed effects and the pre-Dose 1 concentration in NTHi-Mcat-001 study as regressor. The groups will be considered significantly different if the 95% CI for the GMC ratio between the two groups does not contain the value 1. (**Amended 28 June 2018**)

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

Comparison with placebo

Placebo comparative analyses are planned to evaluate the prematurely stopping of the trial.

GMCs and GMC ratios, together with 95% CIs will be computed using a one-way ***ANCOVA*** model on the logarithm 10 transformation of the concentrations/titres. The ***ANCOVA*** model will include the group category as fixed effects and the pre-Dose 1 concentration in NTHi-Mcat-001 study as repressor.

The GMC ratios (vaccinated versus placebo) point estimates obtained from ***ANCOVA*** model will be considered for the evaluation of stopping the trail (section 10.9.2). (**Amended 28 June 2018**)

10.7. Analysis of safety

The safety analysis will be performed on the TVC.

The number of subjects who experienced at least one SAE or any pIMDs during the entire study period will be reported.

The number of subjects who experienced any SAE related to study participation or concurrent GSK medication/ vaccination, during the entire study period, will be reported.

10.8. Interpretation of analyses

Comparative analyses with the aim to characterise the difference in immunogenicity between groups will be descriptive. These descriptive analyses should be interpreted with caution as neither the power nor type I error are controlled for.

10.9. 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.

10.9.1. Sequence of analyses

In this study, three interim analyses (at Visit 1, Visit 1 to Visit 2 and Visit 1 to Visit 4) and one final, cumulative analyses (Visit 1 to Visit 6) will be performed on all subjects:

- The analysis of data at Visit 1 (Month 20) will be performed in a first step. This analysis will include:
  - The analysis of humoral immunogenicity results up to six months (Month 20) following last study visit in NTHi-Mcat-001 study on cleaned data.

This analysis will be documented in a statistical report. Individual listings will be provided at this stage.

- The analysis of data from Visit 1 (Month 20) up to Visit 2 (Month 26) will be performed in a second step. This analysis will include:
  - The analysis of humoral immunogenicity results up to one year (Month 26) following last study visit in NTHi-Mcat-001 study and
  - SAEs and pIMDs up to one year (Month 26) following last study visit in NTHi-Mcat-001 on cleaned data.

This analysis will be documented in a statistical report. Individual listings will be provided at this stage.

- The analysis of data from Visit 1 (Month 20) up to Visit 4 (Month 38) will be performed in a third step. This analysis will include:
  - The analysis of humoral immunogenicity results up to two years (Month 38) following last study visit in NTHi-Mcat-001 study and
  - SAEs and pIMDs up to two years (Month 38) following last study visit in NTHi-Mcat-001 study on cleaned data.

This analysis will be documented in a statistical report. Individual listings will be provided at this stage.

- The analysis from Visit 1 (Month 20) up to Visit 6 (Month 50) will be performed in a fourth step. This analysis will include:
  - The final analysis of all immunogenicity results up to three years (Month 50) following last study visit in NTHi-Mcat-001 study.
  - SAEs and pIMDs up to three years (Month 50) following last study visit on cleaned data.

In addition, all previous analyses will be re-produced based on cleaned data. The final study report will be written only at this point. Individual listings will be provided.

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

Refer to Table 3 for intervals between study visits detailed information. **(Amended 28 June 2018)**

10.9.2. Statistical considerations for interim analyses

No adjustment for multiplicity will be performed for the comparative analyses since they are all descriptive.

At each Interim analysis, primary and secondary objectives will be evaluated and the following stopping rule will be applied: If the GMC ratio (point estimate; Active [10-10-10-AS and 10-10-3-AS groups] vs Placebo) for at least 2 out of 4 antigens is ≤ 2, conclusion of further blood draws and early stop of the trial may be considered.

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 a 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.

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

Not applicable.

13. REFERENCES

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APPENDIX A LABORATORY ASSAYS

Humoral immunity (Amended 28 June 2018)

Serological assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described below and in Table 5. 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).

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 ***25*** EU/mL.

Anti-PilA antibodies

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

Anti-UspA2 antibodies

Anti-UspA2 antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-UspA2 antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ***38*** EU/mL.

APPENDIX B CLINICAL LABORATORIES

Table 10 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

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	204913 (NTHI-MCAT-006 EXT:001)
IND number	16531
EudraCT number	2016-004248-13
Amendment number:	Amendment 1
Amendment date:	Amendment 1 Final: 28 June 2018
Co-ordinating author:	PPD (XPE Pharma & Science for GSK Biologicals)

Rationale/background for changes:

- Table 3 of the protocol (Intervals between study visits) was updated as follow:

  - Optimal length of interval and allowed intervals were updated to avoid the risk of accumulating up to five shortest or longest allowed intervals with possible anticipation/delay of subject's last visit +/– 100 days from the optimal length of the study.

  - Footnote 1 was added to Table 3 to specify that the indication of the month of the visit (i.e. Visit 1 [Month 20]) in the Interval column is an approximate period (label) and not an exact requirement to plan the visit during a specific study month.

  - Footnote 2 was added to Table 3 to define how to count a calendar month for planning the visits.

- The definition of "calendar month" was added to the Glossary of terms.
- The protocol was aligned with the Statistical Analysis Plan Amendment, regarding the model used for the immunogenicity analysis.
- Table 5 and the laboratory assays appendix were updated with new cut-off values, since new optimized assays have been developed during the study. As the ANCOVA model used for the statistical analysis will include the group category as fixed effects and the pre-Dose 1 concentration in NTHi-Mcat-001 study as regressor, it is to be noted that pre-Dose 1 antibody concentrations in NTHi-Mcat-001 study were reported using the first generation ELISA with a cut-off of 7 EL.U/mL. However, the 2 assay versions have been shown to be technically aligned, allowing the exploratory comparison of anti-PilA ELISA data between NTHi-Mcat-001 and NTHi-Mcat-006 studies.
- The list of contributors was updated.
- Minor edits have been made in alignment with GSK protocol template.

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

COVER PAGE

Contributing authors

- PPD ***and*** PPD (Clinical Research & Development Lead***s***)
- PPD ~~and~~***,*** PPD ***and*** PPD PPD (Study Delivery Leads)
- PPD ***and*** PPD (CLS Study manager***s***)
- PPD ***and*** PPD (Study Data Manager***s***)
- PPD ***and*** PPD (Regulatory

Affairs Representative*s*)

LIST OF ABBREVIATIONS

~~**ANOVA**~~ ***ANCOVA***	analysis of ***co***variance

GLOSSARY OF TERMS

Calendar month	***A period from a specified day in one month to the day numerically corresponding to that day in the following month independently on the specific length of the month (i.e. from the 5th of February to the 5th of March)***

Table 3 Intervals between study visits

Interval[1]			Optimal length of interval[2]	Allowed interval
Visit 1 (Month 20)	→	Visit 2 (Month 26)	~~180 days~~ ***6 calendar months after Visit 1 NTHI MCAT 006***	~~160 - 200 days~~ ***±20 elapsed days from optimal planned visit day***
Visit ~~2~~***1*** (Month ~~26~~***20***)	→	Visit 3 (Month 32)	~~180 days~~ ***12 calendar months after Visit 1 NTHI MCAT 006***	~~160 - 200 days~~ ***±20 elapsed days from optimal planned visit day***
Visit ~~3~~***1*** (Month ~~32~~***20***)	→	Visit 4 (Month 38)	~~180 days~~ ***18 calendar months after Visit 1 NTHI MCAT 006***	~~160 - 200 days~~ ***±20 elapsed days from optimal planned visit day***
Visit ~~4~~***1*** (Month ~~38~~***20***)	→	Visit 5 (Month 44)	~~180 days~~ ***24 calendar months after Visit 1 NTHI MCAT 006***	~~160 - 200 days~~ ***±20 elapsed days from optimal planned visit day***
Visit ~~5~~***1*** (Month 44***20***)	→	Visit 6 (Month 50)	~~180 days~~ ***30 calendar months after Visit 1 NTHI MCAT 006***	~~160 - 200 days~~ ***±20 elapsed days from optimal planned visit day***

[1]The indication of the month of the visit, i.e. Visit 1 (Month 20), is an approximate period (label) and not an exact requirement to plan the visit during a specific study month.

[2]Refer to glossary of terms for the definition of the calendar month, in order to plan the visits accordingly. In case a visit occurs on day 31st of a month, the following visit should be planned on the 31st of the 6th subsequent month. If not possible (due to the fact that the following visit is to be planned in a month with less than 31 days) the following visit should be planned on the last day of the 6th subsequent month (i.e. Visit 1: 31 August 2017 Visit 2: 28 February 2018).

Table 4 Biological samples

Sample type	Timepoint	Cohort	N° of subjects	Quantity	Unit
Blood for antibody determination and assay development	Visit 1 (Month 20)	All enrolled subjects	up to 90	~20	ml
	Visit 2 (Month 26)	All enrolled subjects	up to 90	~20	ml
	Visit 3 (Month ~~20~~ ***32***)	All enrolled subjects	up to 90	~20	ml
	Visit 4 (Month 38)	All enrolled subjects	up to 90	~20	ml
	Visit 5 (Month 44)	All enrolled subjects	up to 90	~20	ml
	Visit 6 (Month 50)	All enrolled subjects	up to 90	~20	ml
Total quantity of blood for each subject				~120	mL

Note: Refer to Table 3 for detailed information on intervals between study visits.

Table 5 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit*	Cut-off*	Laboratory**
SERUM	Anti-PD	ELISA	In house	EU/ml	153	GSK Biologicals*** or GSK designated laboratory
SERUM	Anti-PE	ELISA	In house	EU/ml	~~*825*~~	GSK Biologicals*** or GSK designated laboratory
SERUM	Anti-PilA	ELISA	In house	EU/ml	~~*716*~~	GSK Biologicals*** or GSK designated laboratory
SERUM	Anti-UspA2	ELISA	In house	EU/ml	~~*1838*~~	GSK Biologicals*** or GSK designated laboratory

Table 6 Immunological read-outs

Blood sampling time point		No. subjects	Component
Type of contact	Sampling time point		
Visit 1	Month 20	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 2	Month 26	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 3	Month 32	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 4	Month 38	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 5	Month 44	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies
Visit 6	Month 50	up to 90	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2 antibodies

Note: Refer to Table 3 for detailed information on intervals between study visits.

10.6.1. Humoral immune response

Between groups evaluation

The difference in terms of GMCs will be evaluated by computing the 95% CIs of the GMC ratio between groups by using a one-way ~~ANOVA~~ ***ANCOVA*** model on the logarithm10 transformation of the concentrations/ titres. The ~~ANOVA~~ ***ANCOVA*** model will include the group category as fixed effects and the pre-Dose 1 concentration in NTHi-Mcat-001 study as regressor. The groups will be considered significantly different if the 95% CI for the GMC ratio between the two groups does not contain the value 1.

Comparison with placebo

GMCs and GMC ratios, together with 95% CIs will be computed using a one-way ~~ANOVA~~ ***ANCOVA*** model on the logarithm 10 transformation of the concentrations/titres. The ~~ANOVA~~ ***ANCOVA*** model will include the group category as fixed effects and the pre-Dose 1 concentration in NTHi-Mcat-001 study as repressor.

The GMC ratios (vaccinated versus placebo) point estimates obtained from ~~ANOVA~~ ***ANCOVA*** model will be considered for the evaluation of stopping the trail (section 10.9.2).

10.9.1. Sequence of analyses

Refer to Table 3 for intervals between study visits detailed information.

Appendix A LABORATORY ASSAYS

Anti-PE antibodies

Anti-PE antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PE antibodies will be determined, using in-house made reference serum. The technical cut-off of the assay is ~~8~~***25*** EU/mL.

Anti-PilA antibodies

Anti-PilA antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-PilA antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~7~~***16*** EU/mL.

Anti-UspA2 antibodies

Anti-UspA2 antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific anti-UspA2 antibodies will be determined, using an in-house made reference serum. The technical cut-off of the assay is ~~18~~***38*** EU/mL.