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209538 (NTHI MCAT-009)
Protocol Amendment 1 Final

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

Primary Study vaccine	• GSK's non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) multi-antigen vaccine consisting of 3 conserved surface proteins (PD, PE and PilA) from *Haemophilus influenzae* and one conserved surface protein (UspA2) from Mcat (GSK3277511A) adjuvanted with $AS01_E$
Other Study vaccine	• GSK's herpes zoster subunit (HZ/su) (*Shingrix*) vaccine (GSK1437173A), also called VZV gE/AS01B vaccine
eTrack study number and abbreviated title	209538 (NTHI MCAT-009)
Investigational New Drug (IND) number	016531
EudraCT number	2018-002977-24
Date of protocol	Final Version 1: 03 December 2018
Date of protocol amendment/administrative change	Administrative Change 1 Final: 14 December 2018 Amendment 1 Final: 18 May 2020
Title **(Amended 18 May 2020)**	Immunogenicity and safety study of GSK's investigational vaccine (GSK3277511A) when administered in healthy smokers and ex-smokers following receipt of *Shingrix* vaccine.
Detailed Title **(Amended 18 May 2020)**	A Phase IIA, open-label study to evaluate the immunogenicity and safety of sequential use of GSK's investigational vaccine GSK3277511A when administered to healthy smokers and ex-smokers aged 50 to 80 years following receipt of *Shingrix* vaccine.
Co-ordinating author(s)	PPD (XPE Pharma & Science for GSK)
Contributing authors	• PPD (Clinical & Epidemiology Project Lead)

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Contributing authors (Contd.)	• PPD (Clinical Research & Development Lead) • PPD (Study Delivery Lead) • PPD (Lead Statistician) • PPD (Study Statistician***s***) **(Amended 18 May 2020)** • PPD (Clinical Safety Representative) • PPD (Clinical Safety Representative) • PPD (CLS Clinical Read-out Team Leader) • PPD (CLS Study Manager) • PPD (Oversight Data Manager***s***) **(Amended 18 May 2020)** • PPD (Clinical Trials Supply Manager***s***) **(Amended 18 May 2020)** • PPD (Regulatory Affairs Representative) • PPD (Global Patents) • PPD (Lead Science Writer) • PPD (Science Writer)

GSK Biologicals' Protocol DS v 16.0

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209538 (NTHI MCAT-009)
IND number	016531
EudraCT number	2018-002977-24
Date of protocol amendment/administrative change	Amendment 1 Final: 18 May 2020
Detailed Title **(Amended 18 May 2020)**	A Phase IIA, open-label study to evaluate the immunogenicity and safety of sequential use of GSK's investigational vaccine GSK3277511A when administered to healthy smokers and ex-smokers aged 50 to 80 years following receipt of *Shingrix* vaccine.
Sponsor signatory	Ashwani Kumar Arora Clinical & Epidemiology Project Lead
Signature	_____
Date	_____

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)/product(s) and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- 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.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- 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)/product(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 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information 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	209538 (NTHI MCAT-009)
IND number	016531
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Date of protocol amendment/administrative change	Amendment 1 Final: 18 May 2020
Detailed Title **(Amended 18 May 2020)**	A Phase IIA, open-label study to evaluate the immunogenicity and safety of sequential use of GSK's investigational vaccine GSK3277511A when administered to healthy smokers and ex-smokers aged 50 to 80 years following receipt of *Shingrix* vaccine.
Investigator name	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals SA
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 (SAE)

GSK Biologicals' Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.9.3

Study Contact for Reporting SAEs: refer to the local study contact information document.

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

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.5.4.1.

PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Amendment 1	18-MAY-2020
Administrative Change 1	14-DEC-2018
Original Protocol	03-DEC-2018

Amendment 1 18 May 2020

Overall Rationale for the Amendment 1

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

The current analysis of the primary objective is planned on the per-protocol population. The use of the per protocol defined windows for vaccination and blood draws minimizes potential variability within the data for statistical comparisons. The planned analysis would test at least 1 geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. To control the type I error below 2.5% (one-sided), a sequential procedure -is planned in the protocol. Starting from the 6-months lag, the 3-months NI will be tested only if the 6-months NI will be demonstrated, while the 1-month NI will be tested only if the 6-months and 3-months NI will be both demonstrated. The expected sample size would allow to reach 80% of power.

The study started on 23 Apr 2019. At the time of writing, group Sh_NTHi-Mcat**_1** and control group NTHi-Mcat have completed the vaccination schedule and the blood draw as dictated by the study protocol, whereas the less advanced groups (Sh_NTHi-Mcat**_3** and Sh_NTHi-Mcat**_6**) are either due to receive the study vaccine or to undergo a blood draw. In accordance with the safety measures applied for COVID-19 containment in the Countries where the study is conducted, a number of study visits are unlikely to occur as planned. This is expected to impact 2 of the study groups (Sh_NTHi-Mcat**_3** and Sh_NTHi-Mcat**_6**), for which the visits to collect data for primary endpoint are likely to occur while COVID-19 containment measures are in place.

This protocol amendment 1 includes a modified primary objective, should the Sh-NTHI-Mcat_6 **or** the Sh-NTHI-Mcat**_3** and Sh_NTHi-Mcat**_3** groups not meet the per-protocol defined sample size. To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio will be presented for any group not meeting the per protocol sample size using all available data. The descriptive analysis may be used to support the interval between *Shingrix* and NTHi-Mcat vaccines administration for the planned NTHi-Mcat Phase III studies.

This protocol amendment 1 also outlines measures (e.g. for safety monitoring) that may be applicable during special circumstances, like COVID-19 pandemic, in order to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity. However, if the study specific visit and procedures can be completed, then they should be completed according to the protocol, taking into account clinical judgment and local public health guidance to protect the safety of staff and subjects.

In addition, provisions relating to specific reporting of serious adverse events and serious adverse reactions, in accordance with Article R1123-54 and Article R1123-46 of the French Public Health Code, are incorporated into the "Requirements for France" Section of this Protocol Amendment, in order to fulfill the commitment taken with French Health Authority.

Amended text is indicated in ***bold italics*** in the body of the protocol.

Table 2 List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Cover page	To swap the identifiers "short title" and "Detailed Title".	Identifiers need to be corrected
Contributing authors	Addition of new team members	To reflect changes in the Team and contributions to the protocol amendment
Sponsor signature page	To change the identifier "short title" to "Detailed Title".	The detailed title is presented on this page and the identifier needs to be corrected.
Investigator signature page	To change the identifier "short title" to "Detailed Title".	The detailed title is presented on this page and the identifier needs to be corrected.
Section 1 Synopsis; Objectives and endpoints	Modification of the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached, including addition of footnote and update of subsequent footnote referencing.	To add a modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned.
Section 2 Schedule of Activities (SoA) – Table 3 and Table 4	Addition of footnotes: • 11 to add information related to the diagnosis of COVID-19 per the WHO case definition and to clarify that routine study procedures and timeframes for reporting of AEs / SAEs should be followed; and, • 12 to add information regarding alternatives to study contacts	To provide a reference to the WHO case definition for COVID-19, and to clarify that recording of AEs (unsolicited AEs or AEs leading to withdrawal) or SAEs should be aligned with routine procedures for the detection, reporting and recording of AEs or SAEs and timeframes set out in the protocol. And, to add information regarding

Section # and Name	Description of Change	Brief Rationale
	due to special circumstances (e.g. COVID-19 pandemic)	alternatives to study contacts due to special circumstances (e.g. COVID-19 pandemic)
Section 4 Objective(s) and endpoint(s); Table 6 Objectives and endpoints	Modification of the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached, including addition of footnote and update of subsequent footnote referencing.	To add a modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned.
Section 7.5.2 Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses	Correction of typographical error	To correct a minor typographical error to improve readability
Section 8 Study assessments and procedures	Addition of a subsection (Section 8.1) outlining study procedures during special circumstances (e.g. COVID-19 pandemic). (Subsequent Level 2 and Level 3 heading numbering updated.)	To propose alternatives to reduce contacts due to special circumstances (e.g. COVID-19 pandemic): e.g. for safety follow up visits can be replaced by phone calls or virtual contacts, diary cards can be sent back by conventional mail, etc..
Section 8.3.2.1 Blood sampling for immunogenicity assessment / Table 10 and Table 11	Addition of a footnote to clarify study procedures in special circumstances	To highlight alternatives to reduce contacts due to special circumstances (e.g. COVID-19 pandemic): e.g. for safety follow up visits can be replaced by phone calls or virtual contacts, diary cards can be sent back by conventional mail, etc..
Section 8.3.3.1 Humoral antibody responses	Correction of typographical error	To correct a minor typographical error to improve readability
Section 8.3.4.1 Immunological read-outs Table 14	Addition of a footnote to clarify study procedures in special circumstances	To highlight alternatives to reduce contacts due to special circumstances (e.g. COVID-19 pandemic): e.g. for safety follow up visits can be replaced by phone calls or virtual contacts, diary cards can be sent back by conventional mail, etc..
Section 8.4 Safety assessments	Addition of a sentence to clarify reference for case definition and recording of COVID-19 cases	To note that diagnosis of COVID-19 should be aligned with WHO case definition, and routine procedures as outlined in the study protocol for detection, recording and follow-up of AEs/SAEs should be followed

Section # and Name	Description of Change	Brief Rationale
Section 8.4.2 Time period and frequency for collecting AE and serious adverse event (SAE) information (and Table 15 and Table 16)	Addition of footnotes to clarify reference for case definition and recording of COVID-19 cases	To note that diagnosis of COVID-19 should be aligned with WHO case definition, and routine procedures as outlined in the study protocol for detection, recording and follow-up of AEs/SAEs should be followed
Section 10.1.1 Hypotheses related to primary and secondary objectives	Modification of the hypotheses related to the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached.	To include the hypothesis related to the modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned. This is expected to impact 1 or 2 study groups depending on the ongoing viability of visits.
Section 10.1.2 Sample size calculation	Modification of the sample size calculation related to the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached.	To include the sample size calculation related to the modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned. This is expected to impact 1 or 2 study groups depending on the ongoing viability of visits.
Section 10.3.4 Immunogenicity analyses	Modification of the primary objective and detail related to the statistical analyses to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached.	To include the planned immunogenicity analyses in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned. This is expected to impact 1 or 2 study groups depending on the ongoing viability of visits.

Section # and Name	Description of Change	Brief Rationale
Section 12.1.1 List of abbreviations	Addition of COVID-19 and definition	To include a new abbreviation and corresponding definition used in the protocol
Section 12.4.5 Committees Structure	Addition of "No additional information"	To complete an empty section
Section 12.7.3 Requirements for France	Addition of specific provisions relating to specific reporting of serious adverse events and serious adverse reactions in accordance with Article R1123-54 and Article R1123-46 of the French Public Health Code.	To fulfil a commitment with the French Health Authority (ANSM), whereby GSK agreed that the term "issue" included: • suspicions of unexpected serious adverse reactions (SUSAR) occurring in France and outside the national territory; • expected serious adverse reactions and serious adverse events occurring in France; • new facts and urgent security measures.

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1. SYNOPSIS

Indication: Active immunization to reduce exacerbations of chronic obstructive pulmonary disease (COPD) in patients with a history of exacerbations. The population of this study will include healthy smokers and ex-smokers aged 50 to 80 years of age (YOA) which will be used as a proxy for the COPD population.

Rationale: The NTHI MCAT-009 study will provide information regarding the sequential administration of two vaccines adjuvanted with AS01. Specifically, whether a specific time window is required between two different vaccines containing the same AS01 components. The population of this study will include healthy smokers and ex-smokers aged 50 to 80 years of age (YOA) which will be used as a proxy for the COPD population.

Objectives and Endpoints: (Amended 18 May 2020)

Objectives	Endpoints
Primary	
Confirmatory • To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone. *Criterion:* • Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.	• Humoral immune response – Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat groups (Day 181; Day 241; Day 331) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 group:[2]	
Confirmatory ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 months after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone.*** ***Criterion:*** • ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2***	***Humoral immune response*** – ***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_3 group (Day 241) and Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***

Objectives	Endpoints
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups:[3]	
• ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 month after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone.*** ***Criterion:*** ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.***	***Humoral immune response*** ***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***
Secondary	
Descriptive • To evaluate the safety and reactogenicity profile of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when administered alone.	• Solicited local and general adverse events (AEs) – Occurrence of each solicited local and general adverse event (AE), reported during a 7-day follow- up period (i.e. day of vaccination and 6 subsequent days) after Dose 1 and after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine, in all subjects in all groups. • Unsolicited AEs – Occurrence of any unsolicited AEs, reported during a 30-day follow- up period (i.e. day of vaccination and 29 subsequent days) after Dose 1 and after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine, in all subjects in all groups.
	• Serious AEs – Occurrence of any SAE reported from first vaccination (Day 1) to Day 331 in all subjects in all groups. – Occurrence of any SAE, reported from Day 331 to Day 661 in all subjects in all groups. – Potential immune-mediate diseases (pIMD) – Occurrence of any pIMD, reported from first vaccination (Day 1) to Day 331 in all subjects in all groups. – Occurrence of any pIMD, reported from Day 331 to Day 661 in all subjects in all groups.
Descriptive • To describe the humoral immune response of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when administered alone.	• Humoral response – Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations and seropositivity in all subjects before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group).[1,4]

Objectives	Endpoints
Descriptive • To describe the cell mediated immune (CMI) response (CD4+ T-cells) of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when NTHi-Mcat is administered alone, in the CMI response sub-cohort.	• CMI response – NTHi-specific and Mcat-specific CMI responses as measured by flow cytometry ICS (frequency of specific CD4+ T-cells expressing at least 2 different markers among CD40 ligand (CD40L), interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α) upon in vitro stimulation) before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group) in the CMI response sub-cohort.[1]
Tertiary	
Descriptive • To describe the CMI response (CD8+ T-cells) of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when NTHi-Mcat is administered alone, in the CMI response sub-cohort. • To explore the T-helper profile of the PD-, PE-, PilA-, UspA2-specific CD4+/ CD8+ T cell responses.	• CMI response – NTHi-specific and Mcat-specific CMI responses as measured by flow cytometry ICS (frequency of specific CD8+ T-cells expressing at least 2 different markers among CD40L,IL-2, IL-13, IL-17, IFN-γ, TNF-α upon in vitro stimulation) before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group) in the CMI response sub-cohort.[1] • T-helper profile – T-helper profile of the specific T-cell response in T-helper 1, T-helper 2 and T-helper 17 based on the specific expression of respectively IFN- γ, IL-13 and IL-17 before Dose 1 of the NTHi-Mcat investigational vaccine (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat investigational vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group) in the CMI sub-cohort. Frequencies of specific CD4+/CD8+ T cells per 10^6 cells expressing combinations of cytokines/activation markers will be explored.[1]

[1] Given the different intervals between vaccines, the label for study visits or contacts varies between treatment groups. Please refer to the study design diagram.

[2] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 group will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

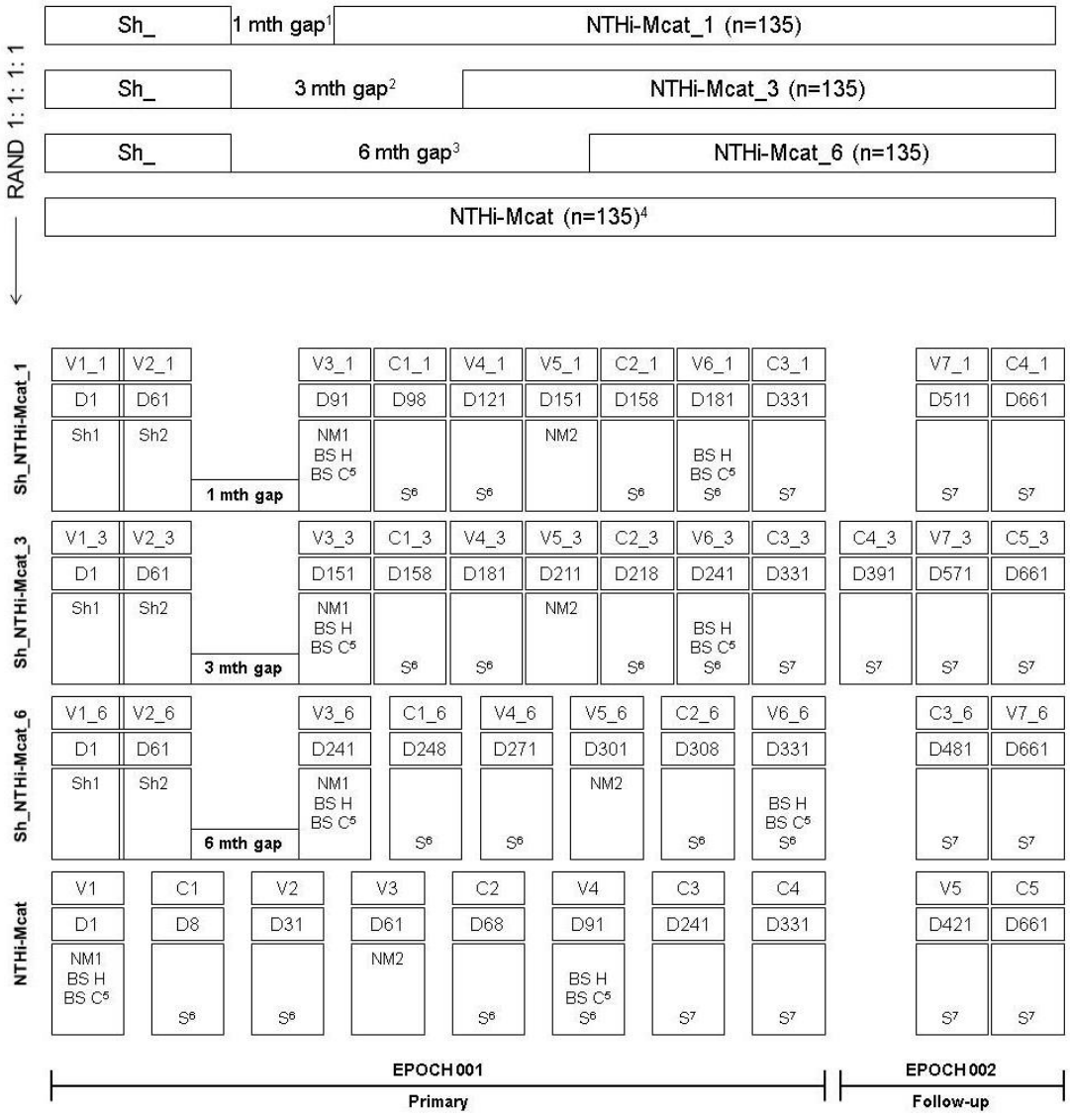
[3] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

[4] Cut-off for seropositivity will be the lower limit of quantification (LLOQ) of the assay.

Overall Design:

A Phase IIA, randomized, open-label, active controlled, multi-centric study with 4 parallel groups (Synopsis Figure 1). Target enrolment is approximately 540 eligible subjects using a 1:1:1:1 randomization ratio (approximately 135 subjects in each of the following groups Sh_NTHi-Mcat_1, Sh_NTHi-Mcat_3, Sh_NTHi-Mcat_6, and NTHi-Mcat). For each subject, the study will last approximately 22 months from Day 1 to study completion (Day 661).

Synopsis Figure 1: Study design



BS C = blood sample for cell-mediated immune response; BS H = blood sample for humoral immune responses/assay development from all subjects; C= Call; D = Day; mth(s) = month(s); NA = not applicable; NM = NTHi-Mcat vaccination; RAND = randomization; S = Safety; Sh = *Shingrix* vaccination; V = Visit

Notes:

1. Groups: Sh_NTHi-Mcat_1 (NTHi-Mcat vaccine administered 1 month after *Shingrix* vaccine)
2. Groups: Sh_NTHi-Mcat_3 (NTHi-Mcat vaccine administered 3 months after *Shingrix* vaccine)
3. Groups: Sh_NTHi-Mcat_6 (NTHi-Mcat vaccine administered 6 months after *Shingrix* vaccine)

4. Subjects randomized to the NTHi-Mcat control group will receive the first NTHi-Mcat vaccination at Visit 1 (Day 1) and the second NTHi-Mcat vaccination at Visit 3 (Day 61)
5. Blood sample for cell-mediated immune response will be taken from approximately 60 subjects (~15 subjects in each group)
6. Solicited local and general adverse events reported during a 7-day follow-up period after Dose 1 and after Dose 2 of NTHi-Mcat vaccine, and unsolicited adverse events reported during a 30-day follow-up period after Dose 1 and after Dose 2 of NTHi-Mcat vaccine will be collected
7. Safety follow-up

2. SCHEDULE OF ACTIVITIES (SOA)

An outline of the study procedures to be performed is provided in Table 3 and Table 4.

Table 3 Schedule of Activities: Sh_NTHi-Mcat groups (Amended 18 May 2020)

		Epoch 001									Epoch 002		
Contact type and contact timepoint by study group	**Sh_NTHi-Mcat_1**	**V1_1 D1**	**V2_1 D61**	**V3_1 D91**	**C1_1 D98**	**V4_1 D121**	**V5_1 D151**	**C2_1 D158**	**V6_1 D181**	**C3_1 D331**	**N/A**	**V7_1 D511**	**C4_1 D661**
	Sh_NTHi-Mcat_3	**V1_3 D1**	**V2_3 D61**	**V3_3 D151**	**C1_3 D158**	**V4_3 D181**	**V5_3[12] D211**	**C2_3 D218**	**V6_3[12] D241**	**C3_3 D331**	**C4_3 D391**	**V7_3[12] D571**	**C5_3 D661**
	Sh_NTHi-Mcat_6	**V1_6 D1**	**V2_6 D61**	**V3_6[12] D241**	**C1_6 D248**	**V4_6[12] D271**	**V5_6[12] D301**	**C2_6 D308**	**V6_6[12] D331**	**N/A**	**C3_6 D481**	**V7_6[12] D661**	**N/A**
Sampling timepoint (vaccinations)		**Sh1**	**Sh2**	**NM1**			**NM2**						
Informed consent		●											
Check inclusion / exclusion criteria		●											
Collect demographic data		●											
Record previous vaccination data		●											
Measure record height and weight		●											
Physical examination[1]		●	O	O			O		O			O	
Smoking status		●											
Smoking exposure history (ATS-DLD-78A questionnaire)		●											
Vaccines													
Study group and treatment number allocation		●											
Treatment number allocation for subsequent doses[2]		O	O	O			O						
Vaccine administration (Sh_NTHi-Mcat groups)[3]		●	●	●			●						
Recording of administered treatment number		●	●	●			●						
Clinical specimens for laboratory assays													
Blood sampling for antibody determination (~10 ml)				●[4]					●				
Blood sampling for CMI response (~40 ml)[5]				●[4]					●				
Safety assessments													
Medical history		●											
Urine pregnancy test[6]		●	●	●			●						
Check contraindications and warnings and precautions to vaccination		O	O	O			O						
Pre-vaccination body temperature		●	●	●			●						
Record any concomitant medication/vaccination[10]		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]
Record any intercurrent medical conditions[10]		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]
Distribution of subject card		O											

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		Epoch 001									Epoch 002		
Contact type and contact timepoint by study group	**Sh_NTHi-Mcat_1**	**V1_1 D1**	**V2_1 D61**	**V3_1 D91**	**C1_1 D98**	**V4_1 D121**	**V5_1 D151**	**C2_1 D158**	**V6_1 D181**	**C3_1 D331**	**N/A**	**V7_1 D511**	**C4_1 D661**
	Sh_NTHi-Mcat_3	**V1_3 D1**	**V2_3 D61**	**V3_3 D151**	**C1_3 D158**	**V4_3 D181**	**V5_3[12] D211**	**C2_3 D218**	**V6_3[12] D241**	**C3_3 D331**	**C4_3 D391**	**V7_3[12] D571**	**C5_3 D661**
	Sh_NTHi-Mcat_6	**V1_6 D1**	**V2_6 D61**	**V3_6[12] D241**	**C1_6 D248**	**V4_6[12] D271**	**V5_6[12] D301**	**C2_6 D308**	**V6_6[12] D331**	**N/A**	**C3_6 D481**	**V7_6[12] D661**	**N/A**
Sampling timepoint (vaccinations)		**Sh1**	**Sh2**	**NM1**			**NM2**						
Distribution of diary cards				O			O						
Return of diary cards						O			O				
Diary card transcription by investigator or delegate						●			●				
Recording of solicited AEs				●	●		●	●					
Recording of unsolicited AEs[11]				●	●	●	●	●	●				
Recording of AEs leading to withdrawal[11]		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]
Recording of SAEs[11] and pregnancies		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]
Recording of pIMDs		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]
Study conclusion												●[9]	●[7]

Note: The double-line borders indicate analyses which will be performed on all data obtained up to those time points.

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

AEs = adverse events; C = Call; CMI = cell-mediated immune response; D = Day; eCRF = electronic case report form; N/A = not applicable; NM = NTHi-Mcat; pIMDs = potential immune-mediated diseases; SAEs = serious adverse events; Sh = *Shingrix*; V = Visit

[1] Complete physical examination including vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate).

[2] Treatment number allocation with randomization at Visit 1 (Day 1) for all treatment groups. Treatment number allocation without randomization at Visit 2 (Day 61), Visit 3 (Day 91; Day 151; Day 241) and, Visit 5 (Day 151; Day 211; Day 301) for Sh_NTHi-Mcat treatment groups (Table 3) and at Visit 3 (Day 61) for NTHi-Mcat treatment group (Table 4).

[3] Vaccinations should be given in the same arm (both *Shingrix* and NTHi-Mcat vaccinations).

[4] Blood sampling must occur prior to vaccination.

[5] Only for subjects in the sub-cohort for CMI (refer to Section 5.3.1 for details regarding the sub-cohort).

[6.] A urine pregnancy test will be performed only for women of childbearing potential.

[7.] Applicable for Sh_NTHi-Mcat_1 and Sh_NTHi-Mcat_3 study groups.

[8.] Applicable for Sh_NTHi-Mcat_3 and Sh_NTHi-Mcat_6 study groups.

[9.] Applicable for Sh_NTHi-Mcat_6 study group.

[10]. **All** concomitant medications/vaccinations and intercurrent medical conditions up to 1 month post Dose 2 of NTHi-MCat vaccine and **all** concomitant medications/vaccinations and intercurrent medical conditions associated with SAEs and pIMDs for the entire study period.

[11] If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (unsolicited AEs, AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 15

[12] Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)

Table 4 Schedule of Activities: NTHi-Mcat group (Amended 18 May 2020)

Epoch	Epoch 001								Epoch 002	
Type of contact	**V1**	**C1**	**V2**	**V3**	**C2**	**V4**	**C3**	**C4**	**V5**	**C5**
Time points	**D1**	**D8**	**D31**	**D61**	**D68**	**D91**	**D241**	**D331**	**D421[9]**	**D661**
Sampling time points	**NM 1**			**NM 2**						
Informed consent	●									
Check inclusion / exclusion criteria	●									
Collect demographic data	●									
Record previous vaccination data	●									
Measure record height and weight	●									
Physical examination[1]	●			O		O			O	
Smoking status	●									
Smoking exposure history (ATS-DLD-78A questionnaire)	●									
Vaccines										
Study group and treatment number allocation	●									
Treatment number allocation for subsequent doses[2]	O			O						
Vaccine administration (NTHi-Mcat group)[3]	●			●						
Recording of administered treatment number	●			●						
Clinical specimens for laboratory assays										
Blood sampling for antibody determination (~10 ml)	●[4]					●				
Blood sampling for CMI response (~40 ml)[5]	●[4]					●				
Safety assessments										
Medical history	●									
Urine pregnancy test[6]	●			●						
Check contraindications and warnings and precautions to vaccination	O			O						
Pre-vaccination body temperature	●			●						
Record any concomitant medication/vaccination[7]	●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions[7]	●	●	●	●	●	●	●	●	●	●

Epoch	Epoch 001								Epoch 002	
Type of contact	**V1**	**C1**	**V2**	**V3**	**C2**	**V4**	**C3**	**C4**	**V5**	**C5**
Time points	**D1**	**D8**	**D31**	**D61**	**D68**	**D91**	**D241**	**D331**	**D421[9]**	**D661**
Sampling time points	**NM 1**			**NM 2**						
Distribution of subject card	O									
Distribution of diary cards	O			O						
Return of diary cards			O			O				
Diary card transcription by investigator or delegate			●			●				
Recording of solicited AEs	●	●		●	●					
Recording of unsolicited AEs	●	●	●	●	●	●				
Recording of AEs leading to withdrawal[8]	●	●	●	●	●	●	●	●	●	●
Recording of SAEs[8] and pregnancies	●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●
Recording of pIMDs	●	●	●	●	●	●	●	●	●	●
Study conclusion										●

Note: The double-line borders indicate analyses which will be performed on all data obtained up to those time points.

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

AEs = adverse events; C = Call; D = Day; eCRF = electronic case report form; NM = NTHi-Mcat; pIMDs = potential immune-mediated diseases; SAEs = serious adverse events; V = Visit; Vacc = vaccination

[1] Complete physical examination including vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate).

[2] Treatment number allocation with randomization at Visit 1 (Day 1) for all treatment groups. Treatment number allocation without randomization at Visit 2 (Day 61), Visit 3 (Day 91; Day 151; Day 241), Visit 5 (Day 151; Day 211; Day 301) for Sh_NTHi-Mcat treatment groups (Table 3) and at Visit 3 (Day 61) for NTHi-Mcat treatment group (Table 4).

[3] Vaccinations should be given in the same arm

[4] Blood sampling must occur prior to vaccination.

[5] Only for subjects in the sub-cohort for CMI (refer to Section 5.3.1 for details regarding the sub-cohort).

[6] A urine pregnancy test will be performed only for women of childbearing potential.

[7] **All** concomitant medications/vaccinations and intercurrent medical conditions up to 1 month post Dose 2 of NTHi-MCat vaccine and **all** concomitant medications/vaccinations and intercurrent medical conditions associated with SAEs and pIMDs for the entire study period

[8] ***If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 15***

[9] ***Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)***

Whenever possible, the investigator should arrange study visits within the intervals described in Table 5.

Table 5 Intervals between study visits

Treatment groups	Interval[1,2]		Optimal length of interval[3]	Allowed interval
Sh_NTHi-Mcat_1[1]	V1_1 (D1) →	V2_1 (D61)	60 days	60 – 80 days[4]
	V2_1 (D61) →	V3_1 (D91)	30 days	30 – 50 days[4]
	V3_1 (D91) →	C1_1 (D98)	7 days	7 – 11 days
	V3_1 (D91) →	V4_1 (D121)	30 days	30 – 45 days
	V3_1 (D91) →	V5_1 (D151)	60 days	60 – 75 days[4]
	V5_1 (D151) →	C2_1 (D158)	7 days	7 – 11 days
	V5_1 (D151) →	V6_1 (D181)	30 days	30 – 45 days[4]
	V5_1 (D151) →	C3_1 (D331)	180 days	180 – 210 days
	V5_1 (D151) →	V7_1 (D511)	360 days	360 – 390 days
	V5_1 (D151) →	C4_1 (D661)	510 days	510 – 540 days
Sh_NTHi-Mcat_3[1]	V1_3 (D1) →	V2_3 (D61)	60 days	60 – 80[4]
	V2_3 (D61) →	V3_3 (D151)	90 days	90 – 110 days[4]
	V3_3 (D151) →	C1_3 (D158)	7 days	7 – 11 days
	V3_3 (D151) →	V4_3 (D181)	30 days	30 – 45 days
	V3_3 (D151) →	V5_3 (D211)	60 days	60 – 75 days[4]
	V5_3 (D211) →	C2_3 (D218)	7 days	7 – 11 days
	V5_3 (D211) →	V6_3 (D241)	30 days	30 – 45 days[4]
	V5_3 (D211) →	C3_3 (D331)	120 days	120 – 150 days
	V5_3 (D211) →	C4_3 (D391)	180 days	180 – 210 days
	V5_3 (D211) →	V7_3 (D571)	360 days	360 – 390 days
	V5_3 (D211) →	C5_3 (D661)	450 days	450 – 480 days
Sh_NTHi-Mcat_6[1]	V1_6 (D1) →	V2_6 (D61)	60 days	60 – 80 days[4]
	V2_6 (D61) →	V3_6 (D241)	180 days	180 – 200 days[4]
	V3_6 (D241) →	C1_6 (D248)	7 days	7 – 11 days
	V3_6 (D241) →	V4_6 (D271)	30 days	30 – 45 days
	V3_6 (D241) →	V5_6 (D301)	60 days	60 – 75 days[4]
	V5_6 (D301) →	C2_6 (D308)	7 days	7 – 11 days
	V5_6 (D301) →	V6_6 (D331)	30 days	30 – 45 days[4]
	V5_6 (D301) →	C3_6 (D481)	180 days	180 – 210 days
	V5_6 (D301) →	V7_6 (D661)	360 days	360 – 390 days

Treatment groups	Interval[1,2]		Optimal length of interval[3]	Allowed interval
NTHi-Mcat[2]	V1 (D1) →	C1 (D8)	7 days	7 – 11 days
	V1 (D1) →	V2 (D31)	30 days	30 – 45 days
	V1 (D1) →	V3 (D61)	60 days	60 – 75 days[4]
	V3 (D61) →	C2 (D68)	7 days	7 – 11 days
	V3 (D61) →	V4 (D91)	30 days	30 – 45 days[4]
	V3 (D61) →	C3 (D241)	180 days	180 – 210 days
	V3 (D61) →	C4 (D331)	270 days	270 – 300 days
	V3 (D61) →	V5 (D421)	360 days	360 – 390 days
	V3 (D61) →	C5 (D661)	600 days	600 – 630 days

D = Day; Sh = *Shingrix*; V = Visit

1. In the Sh_NTHi-Mcat groups, after Day 1 (Visit 1_1; Visit 1_3; Visit 1_6) and Day 61 (Visit 2_1; Visit 2_3; Visit 2_6), the date of Dose 1 (Visit 3_1, Visit 3_3, or Visit 3_6) or Dose 2 (Visit 5_1, Visit 5_3, or Visit 5_6) of the NTHi-Mcat investigational vaccine, respectively, is used as the reference date to define the interval between study visits/contacts.
2. In the NTHi-Mcat groups, the date of Dose 1 (Visit 1) or Dose 2 (Visit 3) of the NTHi-Mcat investigational vaccine, respectively, is used as the reference date to define the interval between study visits/contacts.
3. Whenever possible the investigator should arrange study visits within this interval.
4. Subjects will not be eligible for inclusion in the per protocol set (PPS) for analysis of immunogenicity if the study visit is performed outside this interval

3. INTRODUCTION

3.1. Study rationale

The NTHI MCAT-009 study will provide information regarding the sequential administration of two vaccines adjuvanted with AS01. Specifically, whether a specific time window is required between two different vaccines containing the same AS01 components. The population of this study will include healthy smokers and ex-smokers aged 50 to 80 years of age (YOA) which will be used as a proxy for the COPD population.

3.2. Background

3.2.1. COPD: an introduction

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

The prevalence of COPD is increasing. Worldwide, COPD (GOLD grade II and above) affects 10.1±4.8% of the population ≥40 years of age [Buist, 2007]. COPD is most prevalent in adults/elderly with a history of smoking [Mannino, 2002]. It is the fourth leading cause of chronic morbidity and mortality in the United States and the first in terms of disease burden in China. According to the World Health Organization (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 characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [GOLD, 2017]. 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 colonized with different strains of bacteria [Erb-Downward, 2011; Wilkinson, 2017]. In COPD patients, acquisition of new bacterial strains of a pathogenic bacterial species is believed to be an important cause of AECOPD [Sethi, 2002]. Although estimates vary widely, Non-Typeable *Haemophilus influenzae* (NTHi) appears to be the main bacterial pathogen associated with AECOPD (11–38%), followed by *Moraxella catarrhalis* (Mcat) (3–25%) and *Streptococcus pneumoniae* (4–9%)

[Alamoudi, 2007; Bandi, 2003; Beasley, 2012; Hutchinson, 2007; Ko, 2007; Larsen, 2009; Murphy, 2005; Papi, 2006; Rosell, 2005; Sethi, 2002; Sethi, 2008; Wilkinson, 2006].

3.2.2. Current management of AECOPD

A wide range of pharmacologic (such as inhaled corticosteroids, bronchodilators, phosphodiesterase inhibitors, theophyllines, long-term antibiotics and mucolytics) and non-pharmacologic (such as lung volume reduction surgery, home oxygen, ventilatory support and pulmonary rehabilitation) interventions exist to manage or treat COPD, some with a positive impact on the AECOPD rate. However, a need for further novel interventions remains because current approaches are not completely effective, even when targeted and used optimally.

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

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

3.2.3. GSK Biologicals' NTHi-Mcat investigational vaccine

GlaxoSmithKline (GSK) Biologicals is developing a new NTHi-Mcat investigational vaccine targeting NTHi and Mcat with the aim of reducing the frequency of exacerbations in patients with a history of COPD. The investigational vaccine that will be evaluated in the present study is an adjuvanted multi-component vaccine consisting of conserved surface proteins from NTHi and Mcat. Three NTHi proteins have been selected: Protein D (PD), as a free recombinant protein and Protein E (PE) and type IV pili subunit (PilA) protein, as a recombinant fusion protein named PE-PilA. The selected Mcat antigen is the ubiquitous surface protein A2 (UspA2).

The safety, reactogenicity and immunogenicity of different formulations of the NTHi-Mcat investigational vaccine have been evaluated in the Phase 1 study in healthy adults aged 18-40 years and in current and former smokers aged 50–70 years (study NTHI MCAT-001). Based on results obtained up to 30 days post-Dose 2 from the NTHI MCAT-001 study, the $AS01_E$-adjuvanted formulation containing 10 µg of NTHi proteins PD and PE-PilA and 3.3 µg of UspA2 has been selected for evaluation in the current study.

The adjuvant system $AS01_E$ was developed at GSK Biologicals, and contains 25 µg of the immunostimulants MPL (3-O-desacyl-4'-monophosphoryl lipid A) and 25 µg of QS21 (*Quillaja saponaria* Molina, fraction 21; Antigenics, New York, NY, US) formulated in combination with liposomes. MPL is a chemically detoxified form of the parent lipopolysaccharide from the gram negative bacterium *Salmonella minnesota*. QS21 is a natural saponin molecule (triterpene glycoside) obtained from the tree bark of *Quillaja saponaria* Molina.

The use of an adjuvant may help to induce a higher and longer-lasting immune response in the target population of GSK NTHi-Mcat vaccine; i.e., COPD patients who are often elderly and 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.

3.2.4. GSK Biologicals' *Shingrix* vaccine

Shingrix (Zoster Vaccine Recombinant, Adjuvanted) is approved in the US and in the EU for use in adults 50 years and older for the prevention of HZ (shingles). *Shingrix* is administered as a 2-dose vaccine series (0.5 ml each) as an intramuscular injection. The second dose should be administered anytime between 2 and 6 months after the first dose (refer to Table 5 for optimal (60 days) and allowed intervals (60–80 days) applicable for this study).

The vaccine consists of VZV glycoprotein E (gE) and an adjuvant. The adjuvant system $AS01_B$ is used in combination with the gE antigen. $AS01_B$ and the above-mentioned $AS01_E$ consist of the same components, only the quantities differ. $AS01_B$ contains double the amount (50 µg) of the immunostimulants MPL (3-O-desacyl-4'-monophosphoryl lipid A) and double the amount (50 µg) of QS21 (*Quillaja saponaria* Molina, fraction 21; Antigenics, New York, NY, US) formulated in combination with liposomes.

3.2.5. Sequential administration of AS01 adjuvant vaccines

While substantial data are available to evaluate the safety and immunogenicity of sequential administration of the same AS01-adjuvanted vaccines, evaluation of sequential administration of different AS01-adjuvanted vaccines has not been performed to date.

Available evidence with the RTS,S malaria (up to 4 doses) and HZ candidate vaccines (2 doses) indicates that these AS01-adjuvanted vaccines have a clinically acceptable safety profile, and a positive-benefit–risk ratio, supported by a recent meta-analysis of clinical trials of newly adjuvanted vaccines including AS01 in children, which did not identify any safety concerns [Stassijns, 2016; Didierlaurent, 2017].

Limited clinical trial data are available from subjects who have received multiple administrations of vaccines containing different adjuvanted components. A total of 15 subjects received *Shingrix* and Flu-Ad (flu vaccine adjuvanted with MF59) in the studies Zoster-006 and Zoster-022 [Cunningham, 2018]. The majority of the subjects received *Flu-Ad* more than one year after the last dose of *Shingrix*. From the analysis of the safety listings associated, no specific safety signals were detected for these subjects.

The purpose of this study is to demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) vaccine adjuvanted with $AS01_E$, when administered after vaccination with the AS01-adjuvanted *Shingrix* vaccine (refer to Section 3.1).

3.3. Benefit/Risk assessment

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

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of *Shingrix*.

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

3.3.1. Risk assessment

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk.	Mitigation Strategy
NTHi-Mcat investigational vaccine		
Theoretical risk of acquiring a vaccine-induced autoimmune disease after vaccination.	No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.	Close monitoring of potential immune-mediated diseases (pIMDs) as per study protocol. The potential risk of events of possible autoimmune aetiology occurring is mentioned in the ICF. In addition, the ICF advises subjects to contact the study doctor or the study staff immediately, should they get any symptoms that they feel may be serious.

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk.	Mitigation Strategy
***Shingrix* vaccine**		
Theoretical risk of acquiring a vaccine-induced autoimmune disease after vaccination.	No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.	Close monitoring of pIMDs as per study protocol. The potential risk of events of possible autoimmune aetiology occurring is mentioned in the ICF. In addition, the ICF advises subjects to contact the study doctor or the study staff immediately, should they get any symptoms that they feel may be serious.
Study procedures		
Risk of blood sampling.	Blood sampling associated risk of syncope, dizziness, infection at the site after or during venipuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health (see Section 2 and Section 8.4.2.1).

3.3.2. Benefit assessment

- Contribution to the process of developing of a vaccine against AECOPD.
- Provision of relevant information regarding whether a specific time window is required between two different vaccines containing the same AS01 components.
- Medical evaluations/assessments associated with study procedures (i.e. physical examination).

3.3.3. Overall Benefit: Risk conclusion

Taking into account the measures taken to minimize risks to subjects participating in this study, the potential and/or known risks identified in association with study vaccines (*Shingrix* and NTHi-Mcat) and study procedures, the study vaccines are justified by the anticipated benefits that may be afforded to patients for the prevention of HZ and AECOPD when the 2 vaccine series are sequentially administered with a 1, 3 or 6 month spacing.

4. OBJECTIVE(S) AND ENDPOINT(S)

(Amended 18 May 2020)

Table 6 Study objectives and endpoints

Objectives	Endpoints
Primary	
Confirmatory • To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone. *Criterion:* • Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.	• Humoral immune response – Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat groups (Day 181; Day 241; Day 331) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 group:[2]	
Confirmatory ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 months after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone.*** ***Criterion:*** • ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2***	***Humoral immune response*** – ***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_3 group (Day 241) and Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups:[2]	
• ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 month after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone.***	***Humoral immune response*** ***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***

Objectives	Endpoints
Criterion: ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.***	
Secondary	
Descriptive • To evaluate the safety and reactogenicity profile of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when administered alone.	• Solicited local and general adverse events (AEs) – Occurrence of each solicited local and general adverse event (AE), reported during a 7-day follow- up period (i.e. day of vaccination and 6 subsequent days) after Dose 1 and after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine, in all subjects in all groups. • Unsolicited AEs – Occurrence of any unsolicited AEs, reported during a 30-day follow- up period (i.e. day of vaccination and 29 subsequent days) after Dose 1 and after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine, in all subjects in all groups.
	• Serious AEs – Occurrence of any SAE reported from first vaccination (Day 1) to Day 331 in all subjects in all groups. – Occurrence of any SAE, reported from Day 331 to Day 661 in all subjects in all groups. – Potential immune-mediate diseases (pIMD) – Occurrence of any pIMD, reported from first vaccination (Day 1) to Day 331 in all subjects in all groups. – Occurrence of any pIMD, reported from Day 331 to Day 661 in all subjects in all groups.
Descriptive • To describe the humoral immune response of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when administered alone.	• Humoral response – Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations and seropositivity in all subjects before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group).[1,4]

Objectives	Endpoints
Descriptive • To describe the cell mediated immune (CMI) response (CD4+ T-cells) of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when NTHi-Mcat is administered alone, in the CMI response sub-cohort.	• CMI response – NTHi-specific and Mcat-specific CMI responses as measured by flow cytometry ICS (frequency of specific CD4+ T-cells expressing at least 2 different markers among CD40 ligand (CD40L), interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α) upon in vitro stimulation) before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group) in the CMI response sub-cohort.[1,5]
Tertiary	
Descriptive • To describe the CMI response (CD8+ T-cells) of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when NTHi-Mcat is administered alone, in the CMI response sub-cohort. • To explore the T-helper profile of the PD-, PE-, PilA-, UspA2-specific CD4+/ CD8+ T cell responses.	• CMI response – NTHi-specific and Mcat-specific CMI responses as measured by flow cytometry ICS (frequency of specific CD8+ T-cells expressing at least 2 different markers among CD40L,IL-2, IL-13, IL-17, IFN-γ, TNF-α upon in vitro stimulation) before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group) in the CMI response sub-cohort.[1,4] • T-helper profile – T-helper profile of the specific T-cell response in T-helper 1, T-helper 2 and T-helper 17 based on the specific expression of respectively IFN- γ, IL-13 and IL-17 before Dose 1 of the NTHi-Mcat investigational vaccine (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat investigational vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group) in the CMI sub-cohort. Frequencies of specific CD4+/CD8+ T cells per 10^6 cells expressing combinations of cytokines/activation markers will be explored.[1]

[1] Given the different intervals between vaccines, the label for study visits or contacts varies between treatment groups. Please refer to the study design diagram.

[2] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 group will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

[3] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

[4] Cut-off for seropositivity will be the lower limit of quantification (LLOQ) of the assay.

[5] Refer to Section 5.3.1 for details regarding the CMI response sub-cohort.

5. STUDY DESIGN

5.1. Scientific rationale for study design

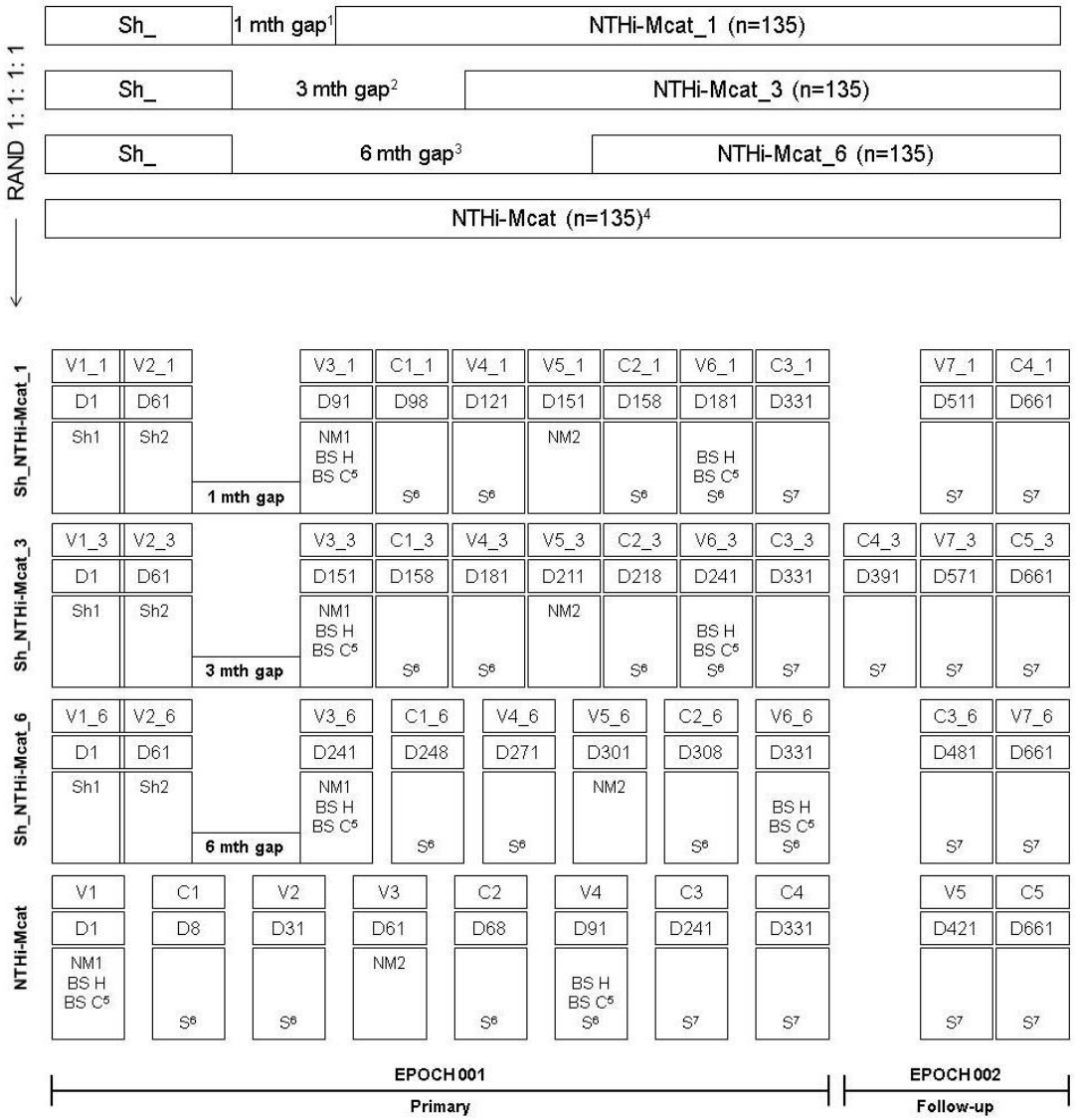
Previous studies in the COPD project have evaluated a 2-dose vaccination schedule in an age range from 40 to 80 years in both healthy subjects either current or former smokers, and COPD patients. The current Phase IIA randomized, open-label study (NTHI MCAT-009), will assess the impact on immunogenicity and safety of the sequential administration of *Shingrix* and the NTHi-Mcat vaccine. Subjects will be given the licensed *Shingrix* vaccine at the approved 2-dose schedule. At 1, 3 or 6 months after the second *Shingrix* vaccine, these subjects will receive the NTHi-Mcat vaccine (2 doses, 2 months apart) (Sh_NTHi-Mcat_1, Sh_NTHi-Mcat_3, Sh_NTHi-Mcat_6 treatment groups). Subjects in the control group will be given the NTHi-Mcat vaccine (2 doses, 2 months apart) alone.

The primary objective of this study is to demonstrate non-inferiority (NI) of the humoral immune response of the NTHi-Mcat vaccine at 1, 3 or 6 months after the *Shingrix* vaccine as compared to the NTHi-Mcat vaccine immune response when prior *Shingrix* has not been received. Secondary objectives include the evaluation of CMI response after the NTHi-Mcat investigational vaccine in a sub-cohort of approximately 60 subjects, and the evaluation of the safety and reactogenicity profile of the NTHi-Mcat vaccine in all subjects.

Shingrix is recommended in the US and in some European countries and based on current data it is anticipated that the vaccine will provide a broad coverage of protection for vaccinated individuals aged 50 years-plus. The planned study population for future COPD efficacy trials includes adults with COPD aged 40 years-plus which has considerable overlap with the *Shingrix* target population. The current study will enroll adults aged 50 to 80 years. As cigarette smoking is the most commonly encountered risk factor for COPD, current and former smokers with a smoking history of at least 10 pack-years will be enrolled in order to immunologically represent the COPD population as much as possible. Data suggest that alterations to the immune system start early on in smokers, before the COPD disease is detected [Barcelo, 2008; Droemann, 2005; Takanashi 1999].

5.2. Overall design

Figure 1 Study design overview



BS C = blood sample for cell-mediated immune response; BS H = blood sample for humoral immune responses/assay development from all subjects; C= Call; D = Day; mth(s) = month(s); NA = not applicable; NM = NTHi-Mcat vaccination; RAND = randomization; S = Safety; Sh = *Shingrix* vaccination; V = Visit

Notes:

1. Groups: Sh_NTHi-Mcat_1 (NTHi-Mcat vaccine administered 1 month after *Shingrix* vaccine)
2. Groups: Sh_NTHi-Mcat_3 (NTHi-Mcat vaccine administered 3 months after *Shingrix* vaccine)
3. Groups: Sh_NTHi-Mcat_6 (NTHi-Mcat vaccine administered 6 months after *Shingrix* vaccine)
4. Subjects randomized to the NTHi-Mcat control group will receive the first NTHi-Mcat vaccination at Visit 1 (Day 1) and the second NTHi-Mcat vaccination at Visit 3 (Day 61)
5. Blood sample for cell-mediated immune response will be taken from approximately 60 subjects (~15 subjects in each group. Refer to Section 5.3.1 for details of the CMI sub-cohort
6. Solicited local and general adverse events reported during a 7-day follow-up period after Dose 1 and after Dose 2 of NTHi-Mcat vaccine, and unsolicited adverse events reported during a 30-day follow-up period after Dose 1 and after Dose 2 of NTHi-Mcat vaccine will be collected
7. Safety follow-up

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 schedule of activities (Section 2), are essential and required for study conduct.

- **Type of study:** self-contained.
- **Experimental design:** Phase IIA , open-label, randomized, controlled, multi-centric, study with 4 parallel groups.
- **Duration of the study:** For each subject, the study will last approximately 22 months from Day 1 to study completion (Day 661).
  - **Epoch 001:** Primary starting at Day 1 and ending at Day 331.
  - **Epoch 002:** Long-term follow-up starting from Day 331 until the end of the study (Day 661).

  Note: Given the intervals between vaccine schedules, the timepoint for study visits or contacts varies between treatment groups (refer to Figure 1).
- **Primary completion date (PCD):** PCD will be 1 month post-Dose 2 of the NTHi-Mcat investigational vaccine (Day 331, based on Sh_NTHi-Mcat_6 treatment group).

Refer to section 12.1.2 for the definition of PCD.

- **End of Study (EoS):** Last subject last visit (Day 661).

Refer to section 12.1.2 for the definition of EoS.

- **Study groups:** Approximately 540 eligible subjects who will be randomly assigned to 4 study groups in a (1: 1: 1: 1) ratio (approximately 135 subjects in each group): Sh_NTHi-Mcat_1, Sh_NTHi-Mcat_3, Sh_NTHi-Mcat_6, NTHi-Mcat. Please refer to Section 10.1 for details related to the determination of sample size.

Table 7 Study groups, treatment and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)	
				Epoch 001 (open-label)	Epoch 002 (open-label)
Sh_NTHi-Mcat_1	135	50 – 80 years	*Shingrix* / NTHi-Mcat	●	●
Sh_NTHi-Mcat_3	135	50 – 80 years	*Shingrix* / NTHi-Mcat	●	●
Sh_NTHi-Mcat_6	135	50 – 80 years	*Shingrix* / NTHi-Mcat	●	●
NTHi-Mcat	135	50 – 80 years	NTHi-Mcat	●	●

Sh = *Shingrix*

- **Control:** active control.

- **Vaccination schedule(s):**
  - **Sh_NTHi-Mcat_1:** 2 doses of GSK Biologicals' *Shingrix* vaccine at Day 1, Day 61 and, following a 1 month gap, 2 doses of GSK Biological's NTHi-Mcat investigational vaccine at Day 91, and Day 151.
  - **Sh_NTHi-Mcat_3:** 2 doses of GSK Biologicals' *Shingrix* vaccine at Day 1, Day 61 and, following a 3 month gap, 2 doses of GSK Biological's NTHi-Mcat investigational vaccine at Day 151 and Day 211.
  - **Sh_NTHi-Mcat_6:** 2 doses of GSK Biologicals' *Shingrix* vaccine at Day 1, Day 61 and, following a 6 month gap, 2 doses of GSK Biological's NTHi-Mcat investigational vaccine at Day 241 and Day 301.
  - **NTHi-Mcat:** 2 doses of GSK Biological's NTHi-Mcat investigational vaccine at Day 1 and Day 61.

  Note: Please refer to Figure 1 for Visit / Contact number.
- **Treatment allocation:** Subjects will be allocated to a study group using an automated, electronic System Built for Internet Randomization (SBIR).
- **Blinding:** open-label.

  Note: Due to the reactogenicity of the *Shingrix* vaccine it is not possible to mask with placebo.
- **Sampling schedule:** Blood samples for the assessment of humoral immunogenicity will be collected from all subjects in all study groups. In addition, blood samples for the assessment of cell-mediated immune (CMI) response will be collected from subjects in the CMI sub-cohort (refer to Section 5.3.1 for details of the CMI sub-cohort). Blood samples will be collected at the following timepoints:
  - **Sh_NTHi-Mcat_1** at Day 91 (Visit 3_1) and Day 181 (Visit 6_1)
  - **Sh_NTHi-Mcat_3** at Day 151 (Visit 3_3) and Day 241 (Visit 6_3)
  - **Sh_NTHi-Mcat_6** at Day 241 (Visit 3_6) and Day 331 (Visit 6_6)
  - **NTHi-Mcat** at Day 1 (Visit 1) and Day 91 (Visit 4).
- **Data collection:** Electronic Case Report Form (eCRF). Telephone contact. Solicited and unsolicited symptoms will be collected using a subject Diary (paper Diary [pDiary]).
- **Safety monitoring:** All subjects will undergo a general physical examination (including vital signs) at Day 1 (Visit 1_1; Visit 1_3; Visit 1_6 in the Sh_NTHi-Mcat groups and Visit 1 in the NTHi-Mcat group), and also during subsequent clinic visits following the NTHi-Mcat vaccination if deemed necessary by the Investigator or delegate. Subjects will be observed for at least 60 minutes after each NTHi-Mcat vaccination for any immediate reactions. Solicited local and general AEs occurring during a 7-day follow-up period after each NTHi-Mcat vaccination (i.e. the day of vaccination and the 6 subsequent days) and unsolicited AEs occurring during a 30-day follow-up period after each NTHi-Mcat vaccination (i.e. the day of vaccination and the 29 subsequent days), will be reported via diary cards. In addition, subjects

will be asked at Phone contacts if there were any safety concerns in the last 7 days; this information will be recorded via the appropriate section of the eCRF. Finally, safety assessments will be performed during each clinic visit and safety follow-up calls to collect information on AEs leading to withdrawal, serious adverse events (SAEs), SAEs related to study participation or to a concurrent GSK medication/vaccine, pregnancies, pIMDs, throughout the study period.

5.3. Number of subjects

Healthy smokers and former smokers aged 50 to 80 years will be enrolled in this study.

A maximum of approximately 540 subjects (135 subjects per study group) will be randomized such that approximately 432 evaluable subjects complete the study (refer to Section 10.1 for a detailed description of the criteria used in the estimation of the sample size).

Withdrawals will not be replaced.

5.3.1. Cell-mediated immune response: sub-cohort

Approximately 60 subjects in total will be part of a **sub-cohort for CMI** analysis (Table 8). An additional blood sample will be taken from these subjects at specified timepoints (pre-Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month post-Dose 2 of the NTHi-Mcat investigational vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group). The CMI sub-cohort will be selected from sites able to process the blood samples according to GSK procedures for peripheral blood mononuclear cell (PBMC) preparation.

Table 8 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
Sub-cohort for CMI	At specific timepoints	
	• Sh_NTHi-Mcat_1 Day 91 (Visit 3_1); Day 181 (Visit 6_1)	~15 subjects
	• Sh_NTHi-Mcat_3 Day 151 (Visit 3_3); Day 241 (Visit 6_3)	~15 subjects
	• Sh_NTHi-Mcat_6 Day 241 (Visit 3_6); Day 331 (Visit 6_6)	~15 subjects
	• NTHi-Mcat Day 1 (Visit 1) and Day 91 (Visit 4)	~15 subjects

CMI = cell-mediated immune response; Sh = *Shingrix*

5.4. Subject and study completion

A subject is considered to have completed the study if he/she returns for the concluding visit/is available for the concluding contact (Day 661 [Call 4_1, Call 5_3, Visit 7_6, Call 5]) as described in the protocol.

6. STUDY POPULATION

6.1. Inclusion criteria for enrolment

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

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject prior to performance of any study specific procedure.
- A male or female between, and including, 50 years and 80 years of age at the time of the first vaccination.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Current or former smoker with a cigarette smoking history ≥10 pack-years.

  Please refer to the glossary of terms for the definitions of pack-years and of current and former smoker.
- Female subjects of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause. Please refer to Section 12.6.1 for definitions of menarche and menopause.
- Female subjects of childbearing potential may be enrolled in the study, if the subject (refer to Section 12.6.1 for definitions of woman of child bearing potential): has practiced adequate contraception for 30 days prior to vaccination (refer to Section 12.6.2 for definition of adequate contraception), and; has a negative pregnancy test on the day of vaccination, and; has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

6.2. 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:

6.2.1. Medical conditions

- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of potential immune-mediated disease (pIMD).

  Note: Please refer to Table 23for a non-exhaustive list of pIMDs. If the subject has any condition on this list, they must be excluded unless the aetiology is clearly documented to be non-immune mediated.

  The investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin and thus meet the exclusion criteria.
- Diagnosis of COPD regardless of severity.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccines. Additionally, consider allergic reactions to other material or equipment related to study participation (such as materials that may possibly contain latex – gloves, syringes, etc).
- Has significant disease (including significant psychological disorders), in the opinion of the investigator, likely to interfere with the study and/or likely to cause death within the study duration.
- History of or current condition preventing intramuscular injection as bleeding or coagulation disorder.
- Malignancies within previous 5 years (excluding non-melanoma skin cancer) or lymphoproliferative disorders.

6.2.2. Prior/concomitant therapy

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the period starting 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of vaccine administration, with the exception of non-MF59 adjuvanted influenza vaccines and pneumococcal vaccines which may be administered ≥15 days preceding or following any study vaccine dose.

  Note: For M59 adjuvanted flu vaccine and for any vaccine containing novel adjuvant refer to exclusion criteria below.
- Planned administration/administration of a vaccine adjuvanted with the following adjuvants AS01, AS02, AS03, AS04 and MF59 in the period starting 6 months before the first dose of study vaccine, and ending at the second blood draw (i.e. approximately 1 month after the administration of the last dose of NTHi-Mcat vaccine). The following non-exhaustive list should be considered as criteria for exclusion: *Prepandrix, Adjupanrix, Shingrix, Fendrix, Cervarix, FluAd, Chiromas, Gripguard*.

- Previous vaccination with any vaccine containing NTHi and/or Mcat antigens.
- Previous vaccination with *Shingrix* (either registered product or participation in a previous vaccine study).
- Previous vaccination with HZ live-attenuated vaccine (ZVL) (either registered product or participation in a previous vaccine study) within the 2 months of the first study visit (Day 1).
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 6 months prior to the first vaccine dose, and ending at the second blood draw (i.e. approximately 1 month after the administration of the last dose of NTHi-Mcat vaccine). For corticosteroids, this will mean prednisone ≥5 mg/day (for adult subjects), or equivalent. Only topical steroids are allowed.
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccine or planned administration starting from Day 1 and ending at the second blood draw (i.e. approximately 1 month after the planned administration of the second dose of NTHi-Mcat vaccine).

6.2.3. Prior/concurrent clinical study experience

- 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 (drug or medical device).

6.2.4. Other exclusions

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- Current alcoholism and/or drug abuse.

  Please refer to the glossary of terms for the definition of alcoholism.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.
- Any study personnel or immediate dependants, family, or household member.

6.3. Criteria for temporary delay for enrolment and vaccination

Vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

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

7. TREATMENTS

Study treatment is defined as a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

7.1. Treatments administered

Table 9 Treatments administered

Study Treatment Name:	***Shingrix***		**NTHi-Mcat**	
Vaccines name	VZV gE	AS01B	NTHi-Mcat 10-10-3	AS01E
Presentation	Lyophilized form in monodose vials	Liquid in monodose vial	Freeze-dried antigens in monodose vial	Liquid in bidose vial
Vaccines formulation:	gE=50µg	MPL=50µg; QS21=50µg; Liposomes	PD=10µg; PE-PilA=10µg; UspA2=3.3µg	MPL=25µg; QS21=25µg; Liposomes
Route of Administration	IM		IM	
Administration site				
Location	Deltoid		Deltoid	
Directionality	Upper		Upper	
Laterality[2]	Non-dominant		Non-dominant	
Number of doses to be administered:	2		2	
Volume to be administered:	0.5 ml		0.5 ml	
Packaging and Labelling	Refer to SPM for more details		Refer to SPM for more details	
Manufacturer	GSK Biologicals SA		GSK Biologicals SA	

AS = adjuvant system; gE = glycoprotein E; MPL = 3-*O*-desacyl-4'-monophosphoryl lipid A; IM = intramuscular; PD = protein D of NTHi; PE= protein E of NTHi*;* PiLA = type IV pili subunit of NTHi*;* QS21 = *Quillaja saponaria Molina*, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation); Sh = *Shingrix*; UspA2 = ubiquitous surface protein A from Mcat; VZV = varicella zoster virus

[1] QS-21: *Quillaja saponaria Molina*, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)

[2] The deltoid of the non-dominant arm is the preferred side of injection. All *Shingrix* and NTHi-Mcat vaccinations should be given in the same arm. In rare cases when it is not possible to inject in the non-dominant arm, injection in the dominant arm may be performed and clearly documented in the eCRF. Subjects who do not receive all Shingrix and NTHi-Mcat vaccinations in the same arm will be excluded from the per protocol analysis.

After completing all prerequisite procedures prior to vaccination (refer to Section 8.3) regarding the contraindications to subsequent vaccination), 1 dose of study reconstituted vaccine will be administered intramuscularly (IM) in the deltoid of the preferably non-dominant arm. Note that Shingrix and NTHi-Mcat vaccinations should be given in the same arm. (Refer to Table 9 for details regarding the treatment administered).

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).

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

7.2. Method of treatment assignment

7.2.1. Subject identification

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

7.2.2. Randomization of treatment

7.2.2.1. Randomization of supplies

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

To allow GSK Biologicals to take advantage of greater rates of recruitment in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

7.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

7.2.2.2.1. Study group and treatment number allocation

The target will be to enrol approximately 540 eligible subjects who will be randomly assigned to 4 study groups in a (1: 1: 1: 1) ratio (approximately 135 subjects in each group) (refer to Section 10.1).

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a minimisation procedure accounting for age category (50–59, 60–69, 70–80 years of age),

smoking status (current or former smoker), and centre. Minimization factors will have equal weight in the minimization algorithm.

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

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

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

7.2.2.2.2. Treatment number allocation for subsequent doses

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

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

7.3. Blinding and unblinding

Data of Epoch 1 and Epoch 2 will be collected in an open manner.

This is an open-label study; however, the specific treatment to be taken by a subject will be assigned using randomization system on internet (MatEx/SBIR). The site will contact the interactive voice/web response system (IVRS/IWRS) or log-on to SBIR prior to the start of study treatment administration for each subject. The site will record the treatment assignment on the applicable Case Report Form, if required. Potential bias will be reduced by central randomization.

7.4. Handling, storage and replacement of study vaccines

7.4.1. Storage and handling of study vaccines

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

A temperature excursion is any temperature that is not in range of the label storage temperature conditions. Temperatures outside the range of label storage temperature conditions must be reported and/or documented. Temperature excursion impacting study vaccines must be reported and/or documented.

In the frame of the reporting, the lack/absence of temperature monitoring documentation from a device meeting GSK requirements has to be considered as a temperature excursion.

Study vaccines that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor).

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

7.4.2. Replacement of unusable vaccines

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 10% additional vaccine/product doses will be supplied to replace those that are unusable.

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

7.5. Concomitant medications/products and concomitant vaccinations

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

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

The following concomitant medications/products/vaccines must be recorded in the eCRF:

- Relevant medications/products, administered starting from Day 1 and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of of NTHi-Mcat study vaccine).
- All concomitant vaccines/medications/products associated with an AE, except vitamins and dietary supplements, administered during the period starting from Day 1 and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of of NTHi-Mcat vaccine).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

Example: An anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥37.5°C]. The preferred location for measuring temperature in this study will be the axilla.

- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the subject from the study. Please refer to Section 7.5.2 for further details.
- Any concomitant medications/products/vaccines relevant to a SAE/potential immune mediated disease (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 a SAE/pIMD need to be recorded on the expedited Adverse Event report.

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

(Amended 18 May 2020)

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 10.2 for populations to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the starting 6 months prior to the first vaccine dose (see ***Section*** 6.2.2) and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of NTHi-Mcat vaccine). For corticosteroids, this will mean prednisone ≥5 mg/day (for adult subjects), or equivalent. Topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Any vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of NTHi-Mcat vaccine),* with the exception of non-MF59 adjuvanted influenza vaccines and pneumococcal vaccines which may be administered ≥15 days preceding or following any study vaccine dose.

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

- Any vaccine adjuvanted with AS01, AS02, AS03, AS04, or MF59, administered until the second blood braw (approximately 30 days after the last dose of NTHi-Mcat vaccine administration).
- Immunoglobulins and/or any blood products administered during the period starting from Day 1 and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of NTHi-Mcat study vaccine).
- Drug and/or alcohol abuse.

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

At each study visit starting from Day 1 and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of NTHi-Mcat vaccine), it must be verified if the subject has experienced or is experiencing any intercurrent medical condition that may lead to elimination from per protocol analysis. If it is the case, the condition(s) must be recorded in the eCRF.

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

7.7. Contraindications to subsequent vaccination

Prior to receipt of additional study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination.

If subjects meet any of the original exclusion/inclusion criteria or the criteria listed below, they should not receive additional vaccinations. Subjects should be encouraged to continue other study procedures at the discretion of the investigator (see Section 8.5.5).

- Subjects who experience any serious adverse event judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 12.5.5.1 for the definition of pIMDs.

7.8. Treatment after completion of the study

Not applicable.

7.9. Screen and baseline failures

Screen failures are not applicable to this study.

Baseline failures may occur where subjects withdraw or are withdrawn following informed consent, but before randomization to study treatment, based on the outcome of the assessment of eligibility versus inclusion and exclusion criteria and physical examination.

8. STUDY ASSESSMENTS AND PROCEDURES

(Amended 18 May 2020)

Study procedures and their timing are summarized in the SoA (Section 2).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject(s) should discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g. blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

8.1. Study procedures during special circumstances

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

- ***Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.***
- ***Diary cards may be transmitted from and to the site by electronic means and or conventional mail.***

8.2. General study aspects

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

8.3. Pre-vaccination procedures

8.3.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. Refer to Section 12.4.3 for the requirements on how to obtain informed consent.

8.3.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 6.1 and 6.2 before enrolment.

8.3.3. Collection of demographic data

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

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

8.3.4. Medical history

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

8.3.5. Smoking status

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

8.3.6. Smoking exposure history

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

Please refer to the SPM for more details on the questionnaire.

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

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

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

8.3.7. Measure/record height and weight

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

8.3.8. Physical examination

At Day 1 (Visit 1_1, Visit 1_3, and Visit 1_6 in the Sh_NTHi-Mcat groups and Visit 1 in the NTHi-Mcat group) perform a complete physical examination of the subject, including vital signs after at least 10 minutes of rest (systolic/diastolic blood pressure, heart rate, respiratory rate). Record collected information in the eCRF.

Physical examination (including vital signs) at Visit 2_1, Visit 2_3, Visit 2_6 up to and including Visit 7_1, Visit 7_3, and Visit 7_6 in the Sh_NTHi-Mcat groups and at Visit 3 up to and including Visit 5 in the NTHi-Mcat group will be performed only if deemed necessary by the Investigator or delegate.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the allowed interval for this visit (see Table 5).

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

8.3.9. Urine pregnancy test

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

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

8.3.10. Previous vaccination

At Day 1 (Visit 1_1, Visit 1_3, and Visit 1_6 in the Sh_NTHi-Mcat groups and Visit 1 in the NTHi-Mcat group), previous vaccination history must be recorded.

Please refer to Section 7.5 for details on the management of concomitant vaccination during the study.

8.3.11. Check contraindications to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Section 7.7 for more details.

8.3.12. Pre-vaccination body temperature

The axillary body temperature of each subject needs to be measured prior to any study vaccine administration. If the subject has fever [fever is defined as temperature ≥37.5°C] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (Table 5).

8.3.13. Distribution of Subject Card

For information regarding the Subject Card, please refer to Section 8.5.7.

8.3.14. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 7.2.2.2.1. The number of each administered treatment must be recorded in the eCRF.

8.3.15. Study vaccine administration

After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) preferably in the deltoid of the non-dominant arm (refer to Section 7.1 for detailed description of the vaccine administration procedure).

All *Shingrix* and NTHi-Mcat vaccinations should be given in the same arm for the same subject.

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).

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

8.4. Immunogenicity assessments

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 in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

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

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

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

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

8.4.1. Use of specified study materials

When materials are provided by GSK Biologicals or GSK Biologicals' designated 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 10.2 for the definition of populations for analyses). 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 GSK Biologicals' designated 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.

8.4.2. Biological samples

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.

8.4.2.1. Blood sampling for immunogenicity assessments

Blood samples will be taken during certain study visits as specified in Section 2 Schedule of Activities (SoA). First blood sampling should occur prior to the first NTHi-Mcat vaccine administration.

From all subjects included in the immunogenicity sub-cohort (refer to Section 5.3.1) an overall volume of 50 ml of whole blood should be drawn to allow both the analysis of humoral immune response and the analysis of CMI response at each pre-defined timepoint (see sections below).

Blood samples for humoral immunogenicity

(Amended 18 May 2020)

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

Table 10 Blood sampling for humoral immunogenicity

Sample type	Quantity	Unit	Study group	Timepoint[1]	Subjects
Blood for humoral immunogenicity	~10	ml	Sh_NTHi-Mcat_1	D91 (V3_1) D181 (V6_1)	All subjects in study group
			Sh_NTHi-Mcat_3	D151 (V3_3) D241 (V6_3)	All subjects in study group
			Sh_NTHi-Mcat_6	D241 (V3_6) D331 (V6_6)	All subjects in study group
			NTHi-Mcat	D1 (V1) D91 (V4)	All subjects in study group

D = Day; Sh = *Shingrix*; ml = millilitres; V = Visit

[1] ***Refer also to Schedule of Activities (Table 3 and Table 4), and Section 8.1 for information on study procedures during special circumstances***

Blood samples for CMI

(Amended 18 May 2020)

A volume of approximately 40 ml of whole blood should be drawn from all subjects included in the immunogenicity sub-cohort for analysis of CMI response at each pre-defined timepoint (Table 11). The samples should be kept at room temperature and should be shipped as soon as possible so that the CMI laboratory can start cell separation processing within 24 hours of collection. Refer to the SPM and Central Laboratory manual for more details on sample storage conditions.

Table 11 Blood sampling for CMI

Sample type	Quantity	Unit	Study group	Timepoint[2]	Subjects
Blood for CMI	~40	ml	Sh_NTHi-Mcat_1	D91 (V3_1) D181 (V6_1)	Sub-cohort for CMI[1]
			Sh_NTHi-Mcat_3	D151 (V3_3) D241 (V6_3)	Sub-cohort for CMI[1]
			Sh_NTHi-Mcat_6	D241 (V3_6) D331 (V6_6)	Sub-cohort for CMI[1]
			NTHi-Mcat	D1 (V1) D91 (V4)	Sub-cohort for CMI[1]

CMI = cell-mediated immune response; D = Day; Sh = *Shingrix*; ml = millilitres; V = Visit

Notes:

[1] Refer to Section 5.3.1 for details regarding the CMI sub-cohort

[2] ***Refer also to Schedule of Activities Table 3 and Table 4), and Section 8.1 for information on study procedures during special circumstances***

8.4.3. Laboratory assays

Please refer to Appendix 2 for a detailed description of the assays performed in the study. Please refer to Appendix 3 for the address of the clinical laboratories used for sample analysis.

8.4.3.1. Humoral antibody responses

Total IgG concentrations will be measured by ELISA at GSK Biologicals' laboratory (i.e. Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany), or a GSK designated laboratory using qualified procedures (refer to Table 10).

Table 12 Humoral immunity (antibody determination)

System	Component	Method	Kit/Manufacturer	Unit[1]	Assay cut-off[1]	Laboratory[2]
SERUM	anti-PD antibody	ELISA	In-house	EU/mL	153	GSK Biologicals[3] or GSK designated laboratory
SERUM	anti-PE antibody	ELISA	In-house	EU/mL	25	GSK Biologicals[3] or GSK designated laboratory
SERUM	anti-PilA antibody	ELISA	In-house	EU/mL	16	GSK Biologicals[3] or GSK designated laboratory
SERUM	anti-UspA2 IgG antibody	ELISA	In-house	EU/mL	38	GSK Biologicals[3] or GSK designated laboratory

ELISA = Enzyme Linked Immunosorbent Assay; EU/ml = ELISA unit per millilitre; Ig = immunoglobulin; PD = protein D; from NTHi; PE = protein E from NTHi; PilA = type IV pili subunit from NTHi; UspA2 = ubiquitous surface protein A2 from Mcat

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

2 Refer to Appendix 7 for the laboratory addresses.

3 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 of measuring the immune response to any component of either the NTHi-Mcat investigational vaccines and/or to other respiratory pathogens. The research may include, but is not limited to**,** functional assays such as serum bactericidal activity assays against NTHi and/or Mcat. **(Amended 18 May 2020)**

8.4.3.2. Cell-mediated immune response

CMI assays will be performed at GSK Biologicals or GSK designated laboratory using optimised or qualified procedures (Table 13).

Table 13 CMI using flow cytometry

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

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

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

Additional testing on peripheral blood mononuclear cells (PBMCs), such as, but not limited to, evaluation of NTHi and/or Mcat-specific memory B-cells, intracellular cytokine staining (ICS) testing assessing other markers such as 41BB or using other

bacterial antigens, may be done during the study or after study completion, should these data be required for accurate interpretation of the data and/ or for further research related to the investigational vaccine and/ or the disease, should such test(s) become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Additional 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.

8.4.4. Biological samples evaluation

8.4.4.1. Immunological read-outs

(Amended 18 May 2020)

Table 14 Immunological read-outs

Blood sampling timepoint		Study group	No. subjects	Component
Type of contact and timepoint[3]	Sampling timepoint			
D91 (V3_1)	Pre NTHi-Mcat Vacc I	Sh_NTHi-Mcat_1	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells
D151 (V3_3)	Pre NTHi-Mcat Vacc I	Sh_NTHi-Mcat_3	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells
D241 (V3_6)	Pre NTHi-Mcat Vacc I	Sh_NTHi-Mcat_6	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells
D1 (V1)	Pre NTHi-Mcat Vacc I	NTHi-Mcat	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells
D181 (V6_1)	Post NTHi-Mcat Vacc II	Sh_NTHi-Mcat_1	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells
D241 (V6_3)	Post NTHi-Mcat Vacc II	Sh_NTHi-Mcat_3	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells
D331 (V6_6)	Post NTHi-Mcat Vacc II	Sh_NTHi-Mcat_6	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells
D91 (V4)	Post NTHi-Mcat Vacc II	NTHi-Mcat	All[1] (~135)	Anti-PD, Anti-PE, Anti-PilA and Anti-UspA2
			CMI sub-cohort (~15[2])	Specific CD4+/CD8+ T-cells

PD = protein D from NTHi; PE = protein E from NTHi; PilA = type 4 pili subunit from NTHi; Sh = *Shingrix*; UspA2 – ubiquitous surface protein A2 from Mcat; V=Visit ; Vacc= vaccination

[1] All subjects in the study group specified

[2] Subjects in the study group specified in the CMI sub-cohort. Refer to Section 5.3.1 for details regarding the sub-cohort for CMI response

[3] ***Refer also to Schedule of Activities (Table 3 and Table 4), and Section 8.1 for information on study procedures during special circumstances***

8.4.5. Immunological correlates of protection

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

8.5. Safety Assessments

(Amended 18 May 2020)

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Diagnosis of COVID-19 should be made in accordance with the WHO case definition. Cases should be categorised as AEs (unsolicited or AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 15 and Table 16.

The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the NTHI MCAT-009 study.

8.5.1. Safety definitions

Please refer to Section 12.5 for safety definitions.

8.5.2. Time period and frequency for collecting AE and serious adverse event (SAE) information

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 15and Table 16.

Refer to the Section 12.5.8.1 for details on the time period for recording safety information.

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 15and Table 16.

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

Table 15 Reporting periods for collecting safety information: Sh_NTHi-Mcat groups (Amended 18 May 2020)

Event	Study group	Contact type (V/C) and timepoint (D)											
	Sh_NTHi-Mcat_1	V1_1 D1	V2_1 D61	V3_1 D91	C1_1 D98	V4_1 D121	V5_1 D151	C2_1 D158	V6_1 D181	C3_1 D331	V7_1 D511	N/A	C4_1 D661
	Sh_NTHi-Mcat _3	V1_3 D1	V2_3 D61	V3_3 D151	C1_3 D158	V4_3 D181	V5_3** D211	C2_3 D218	V6_3** D241	C3_3 D331	C4_3** D391	V7_3** D571	C5_3 D661
	Sh_NTHi-Mcat _6	V1_6 D1	V2_6 D61	V3_6** D241	C1_6 D248	V4_6** D271	V5_6** D301	C2_6 D308	V6_6** D331	N/A	C3_6 D481	N/A	V7_6** D661
Solicited local and general AEs	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat_3 Sh_NTHi-Mcat_6												
Unsolicited AEs*	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat_3 Sh_NTHi-Mcat_6												
AEs/SAEs leading to withdrawal from the study*	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat_3 Sh_NTHi-Mcat_6												
SAEs*	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat_3 Sh_NTHi-Mcat_6												
SAEs related to study participation or concurrent GSK medication/vaccine	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat_3 Sh_NTHi-Mcat_6												

Event	Study group	Contact type (V/C) and timepoint (D)											
	Sh_NTHi-Mcat_1	**V1_1 D1**	**V2_1 D61**	**V3_1 D91**	**C1_1 D98**	**V4_1 D121**	**V5_1 D151**	**C2_1 D158**	**V6_1 D181**	**C3_1 D331**	**V7_1 D511**	**N/A**	**C4_1 D661**
	Sh_NTHi-Mcat _3	**V1_3 D1**	**V2_3 D61**	**V3_3 D151**	**C1_3 D158**	**V4_3 D181**	**V5_3** D211**	**C2_3 D218**	**V6_3** D241**	**C3_3 D331**	**C4_3** D391**	**V7_3** D571**	**C5_3 D661**
	Sh_NTHi-Mcat _6	**V1_6 D1**	**V2_6 D61**	**V3_6** D241**	**C1_6 D248**	**V4_6** D271**	**V5_6** D301**	**C2_6 D308**	**V6_6** D331**	**N/A**	**C3_6 D481**	**N/A**	**V7_6** D661**
Pregnancies	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat_3 Sh_NTHi-Mcat_6												
pIMDs	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat_3 Sh_NTHi-Mcat_6												

AEs = adverse events; C = Call; D = Day; N/A = not applicable; pIMDs= potential immune mediated diseases; SAEs = serious adverse events; Sh = *Shingrix*; V = Visit

**** If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (unsolicited AEs, AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the defined time period***

***** Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)***

Table 16 Reporting periods for collecting safety information: NTHi-Mcat group (Amended 18 May 2020)

Event	Contact type (V/C) and timepoint (D)									
	V1 D1	C1 D8	V2 D31	V3 D61	C2 D68	V4 D91	C3 D241	C4 D331	V5** D421	C5 D661
Solicited local and general AEs										
Unsolicited AEs										
AEs/SAEs leading to withdrawal from the study*										
SAEs*										
SAEs related to study participation or concurrent GSK medication/vaccine*										
Pregnancies										
pIMDs										

AEs = adverse events; C = Call; D = Day; N/A = not applicable; pIMDs= potential immune mediated diseases; SAEs = serious adverse events; V = Visit

**** If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the defined time period***

***** Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)***

8.5.3. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5.8.

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

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

SAEs that occur in the time period defined in Section 8.5.2 will be reported promptly to GSK within the timeframes described in Table 17once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.5.2 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 8.5.2 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 17 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

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

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

8.5.4.1. Contact information for reporting of serious adverse events (SAEs), pIMDs and pregnancies

Table 18 Contact information for reporting of serious adverse events (SAEs), pIMD and pregnancies

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

8.5.4.2. Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential for meeting legal obligations and ethical responsibilities for the safety of subjects and the safety of a study treatment under clinical investigation.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and pIMDs (serious or non-serious) will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.5.11.

8.5.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE/pIMDs should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.5).

8.5.7. Subject card

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

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

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

8.6. Holding rules and safety monitoring

Not applicable.

8.7. Genetic research (pharmacogenetics)

Genetics are not evaluated in this study.

8.8. Biomarkers and pharmacogenomics

Not applicable.

8.9. Economic assessment

Not applicable.

9. DISCONTINUATION CRITERIA

9.1. Discontinuation 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/was not available for the concluding contact foreseen in the protocol.

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

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

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

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

- Adverse events requiring expedited reporting (refer to Section 12.5.9.2)
- Unsolicited non-serious adverse event
- Solicited adverse event
- Protocol deviation
- Withdrawal by subject, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 12.5.11).

9.2. Discontinuation of study vaccines

A 'withdrawal' from the study vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccines may continue further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

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

- Adverse event requiring expedited reporting
- Non-serious adverse event (specify)
- Unsolicited non-serious adverse event
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

9.3. Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

10.1.1. Hypotheses related to primary and secondary objectives

(Amended 18 May 2020)

The global null hypothesis related to the primary objective of the study is that at least one geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. This must be rejected in favour of the alternative hypothesis that all 4 GMCs (anti-PD, anti-PE, anti-PilA, anti-UspA2) are non-inferior in at least one time-lag group.

As defined in the study criteria of success, non-inferiority (NI) will be claimed for a specific time-lag if the lower limit of the 2-sided 95% CI of the GMC ratio (Sh_NTHi-Mcat_**k** over NTHi-Mcat, where **k**= [6, 3, 1]) will be above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA and anti-UspA2 concentration. Family-wise type I error is fixed at 2.5% (1-sided).

If the per-protocol sample size is either not reached in the Sh_NTHi-Mcat_6 group or not reached in the Sh_NTHi-Mcat_6 and in Sh_NTHi-Mcat_3 groups due to COVID-19 containment measures, a modification to the primary objective will be applied as follows:

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 due to COVID-19 containment measures:***

  The global null hypothesis related to the primary objective of the study is that at least 1 GMC ratio (Sh_NTHi-Mcat_k, where k=3 or 1 over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. This must be rejected in favour of the alternative hypothesis that all 4 GMCs (anti-PD, anti-PE, anti-PilA, anti-UspA2) are non-inferior in at least one time-lag group.

  As defined in the study criteria of success, non-inferiority (NI) will be claimed for a specific time-lag if the lower limit of the 2-sided 95% CI of the GMC ratio (Sh_NTHi-Mcat_k over NTHi-Mcat, where k= [3, 1]) will be above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA and anti-UspA2 concentration. Family-wise type I error is fixed at 2.5% (1-sided).

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 and Sh_NTHI-Mcat_3 due to COVID-19 containment measures:***

  The global null hypothesis related to the primary objective of the study is that the GMC ratio (Sh_NTHi-Mcat_1 over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. This must be rejected in favour of

the alternative hypothesis that all 4 GMCs (anti-PD, anti-PE, anti-PilA, anti-UspA2) are non-inferior.

As defined in the study criteria of success, non-inferiority (NI) will if the lower limit of the 2-sided 95% CI of the GMC ratio (Sh_NTHi-Mcat_1 over NTHi-Mcat) will be above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA and anti-UspA2 concentration. Family-wise type I error is fixed at 2.5% (1-sided).

10.1.2. Sample size calculation

(Amended 18 May 2020)

The study sample size is defined in order to ensure a global 80% power to conclude NI on all anti-PD, anti-PE, anti-PilA and anti-UspA2 for at least one time-lag. The target response-wise power is then 94.6%, assuming independence, for the 4 antigens response. The sample size calculation is based on a standard deviation of antibody $\log_{10}$-concentrations of 0.36 (based on NTHI MCAT-001) and a null true difference on the $\log_{10}$ scale.

To control the type I error below 2.5% (one-sided), a sequential procedure will be used for the primary objective. Starting from the 6-months lag, the 3-months NI will be tested only if the 6-months NI will be demonstrated, while the 1-month NI will be tested only if the 6-months and 3-months NI will be both demonstrated. Sequential testing procedure ensures also 80% power to conclude NI for each time-lag (i.e. conditionally on demonstrating NI at previous steps of the procedure). The power to prove all NI hypotheses is 51% (assuming independence).

The target sample size is 432 subjects evaluable for immunogenicity (108 subjects per study group). 'Evaluable subjects' means all subjects included in the set for the primary statistical analysis defined in Section 10.2. Considering that approximately 20% of the randomized subjects might withdraw, not be evaluable for immunogenicity or be excluded due to protocol deviations, the target sample size to be randomized is 540 subjects (135 subjects per study group).

If the per-protocol sample size is either not reached in the Sh_NTHi-Mcat_6 group or not reached in the Sh_NTHi-Mcat_6 and in Sh_NTHi-Mcat_3 groups due to COVID-19 containment measures, a modification to the primary objective will be applied as follows:

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 due to COVID-19 containment measures:***

  To control the type I error below 2.5% (one-sided), a sequential procedure will be used for the primary objective. Starting from the 3-months lag, while the 1-month NI will be tested only if the 3-months NI will be demonstrated. Sequential testing procedure ensures also 80% power to conclude NI for each time-lag (i.e. conditionally on demonstrating NI at previous steps of the procedure). The power to prove all NI hypotheses is 64% (assuming independence).

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 due to COVID-19 containment measures:***

  The power to prove the NI hypothesis is 80%.

10.2. Populations for analyses

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled	All subjects who sign informed consent
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Full analysis	All subjects who received at least 1 dose of the study treatment and have post-vaccination immunogenicity data
Modified full analysis (mFAS)	All subjects who received full study treatment course to which they are randomized and have post-vaccination immunogenicity data
Per protocol	All subjects who received full study treatment course to which they are randomized and have post-vaccination data (mFAS) minus subjects with protocol deviations that lead to exclusion*
Unsolicited safety	All subjects who received at least 1 dose of the study treatment (exposed set) that report unsolicited AEs or that report not having unsolicited AEs
Solicited safety	All subjects who received at least 1 dose of the study treatment (exposed set) who have solicited safety data

10.3. Statistical analyses

10.3.1. Subjects disposition

Number of enrolled, and number of vaccinated (at least 1 vaccination and full vaccination course) subjects, included in each group or in total will be described. These might be additionally broken down by country and/or by site.

10.3.2. Demography and baseline characteristics analyses

Demographic characteristics (including age at first study vaccination in years, gender, race, ethnicity and smoking status) will be summarized by study groups and overall, using descriptive statistics:

- Frequency tables will be generated for categorical variables such as smoking status.
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age, height and weight.

Withdrawal status will be summarized by group using descriptive statistics:

- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal
- The number of subjects enrolled into the study as well as the number of subjects excluded from the per protocol set (PPS) and mFAS will be tabulated.

10.3.3. Efficacy analyses

Not applicable.

10.3.4. Immunogenicity analyses

(Amended 18 May 2020)

The primary analysis will be based on the PPS. A supplementary analysis may be based on the mFAS.

Endpoint	Statistical analysis methods
Primary Endpoint(s)	
Primary	**Between group assessment** Considering the sampling timepoint at 1 month after Dose 2 of NTHi-Mcat vaccine, the 2-sided 95% CIs for the group GMC ratio (Sh_NTHi-Mcat_1; _3; _6 group over NTHi-Mcat group) of anti-PD, anti-PE, anti-PilA, anti-UspA2 will be computed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations. The ANCOVA model will include study group, smoking status (current or former), age category (50–59, 60–69, 70–80 years of age) and centre as factors and the antibody concentration before Dose 1 as covariate. Non-inferiority for a specific time-lag will be claimed if the lower limit of the 2-sided 95% CI for the GMC ratio will be above 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2. The sequential procedure for multiple time-lags will be used: starting from the 6-months lag, the 3-months NI will be tested only if the 6-months NI will be demonstrated, while the 1-month NI will be tested only if the 6-months and 3-months NI will be both demonstrated.
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 group:[1]	***Considering the sampling timepoint at 1 month after Dose 2 of NTHi-Mcat vaccine, the 2-sided 95% CIs for the group GMC ratio (Sh_NTHi-Mcat_1; _3 group over NTHi-Mcat group) of anti-PD, anti-PE, anti-PilA, anti-UspA2 will be computed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations. The ANCOVA model will include study group, smoking status (current or former), age category (50–59, 60–69, 70–80 years of age) and centre as factors and the antibody concentration before Dose 1 as covariate.*** ***Non-inferiority for a specific time-lag will be claimed if the lower limit of the 2-sided 95% CI for the GMC ratio will be above 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2. The sequential procedure for multiple time-lags will be used: starting from the 3-months lag, the 1-month NI will be tested only if the 3-months NI will be demonstrated.***

Endpoint	Statistical analysis methods
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 and the Sh_NTHi-Mcat_3 groups:[2]	***Considering the sampling timepoint at 1 month after Dose 2 of NTHi-Mcat vaccine, the 2-sided 95% CIs for the group GMC ratio (Sh_NTHi-Mcat_1 group over NTHi-Mcat group) of anti-PD, anti-PE, anti-PilA, anti-UspA2 will be computed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations. The ANCOVA model will include study group, smoking status (current or former), age category (50–59, 60–69, 70–80 years of age) and centre as factors and the antibody concentration before Dose 1 as covariate.*** ***Non-inferiority for a specific time-lag will be claimed if the lower limit of the 2-sided 95% CI for the GMC ratio will be above 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.***
Secondary Endpoint(s)	
Secondary - humoral	**Within group assessment** For each study group, for each sampling timepoint and for each antigen, the following statistics will be computed: • Seropositivity rates with exact 95% CI (seropositivity defined using the assay lower limits of quantification [LLOQ]) • Adjusted and unadjusted GMCs with 95% CI (adjustment by ANCOVA model, as specified above) • The range and distribution of antibody concentrations The distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves.
Secondary –cell-mediated immune response	CMI response induced by the NTHi-Mcat candidate vaccine will be evaluated, presenting the frequencies of antigen-specific CD4+ T cells per 10^6 cells. The specific CD4+ T cells being identified as the CD4 + T cells expressing at least 2 different markers among CD40 Ligand (CD40L), IL-2, TNF- α, IFN- γ, IL-13 and IL-17 upon in vitro stimulation. Descriptive statistics (Min, Q1, Median, Mean, Q3 & Max) will be reported for each group at pre-Dose 1 of the NTHi-Mcat investigational vaccine (Day 91; Day 151; Day 241 in the Sh-NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat investigational vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group).
Tertiary –cell-mediated immune response	• CMI response induced by the NTHi-Mcat candidate vaccine will be evaluated, presenting the frequencies of antigen-specific CD8+T cells per 10^6 cells. The specific CD8+T cells being identified as the CD8+ T cells expressing at least 2 different markers among CD40L, IL-2, TNF- α, IFN- γ, IL-13 and IL-17 upon in vitro stimulation. • CMI response as the frequencies of specific CD4+/CD8+ T cells per 10^6 cells expressing any combination of cytokines/activation markers will be determined. The T-helper profile of the specific T-cell response in T-helper 1, T-helper 2 and T-helper 17 based on the specific expression of respectively IFN- γ, IL-13 and IL-17 will be characterized. Descriptive statistics (Min, Q1, Median, Mean, Q3 & Max) will be reported for each group at pre-Dose 1 of the NTHi-Mcat investigational vaccine (Day 91; Day 151; Day 241 in the Sh-NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat investigational vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group).

[1] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 group will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

[2] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

10.3.5. Safety analyses

All safety analyses will be performed on the solicited safety set, unsolicited safety set and exposed set.

Endpoint	Statistical analysis methods
Secondary	**Within group assessment** The percentage of subjects with at least 1 local adverse event (AE) (solicited and unsolicited), with at least 1 general AE (solicited and unsolicited) and with any AE during the 7-days solicited follow-up period and the 30-days follow-up period will be tabulated by group with exact 95% CI after each NTHi-Mcat vaccine dose and overall. The percentage of NTHi-Mcat doses followed by at least 1 local AE (solicited and unsolicited), by at least 1 general AE (solicited and unsolicited) and by any AE will be tabulated by group with exact 95% CI. The same calculations will be performed for AEs rated as Grade 3, for AEs causally related to vaccination and Grade 3 AEs causally related to vaccination. The percentage of subjects reporting each individual solicited local and general AE during the 7-days solicited follow-up period after each dose of NTHi-Mcat vaccine will be tabulated by group with exact 95% CI. The percentage of NTHi-Mcat doses followed by each individual solicited local and general AE will be tabulated by group with exact 95% CI. Fever will be reported per 0.5°C cumulative increments. For all solicited symptoms, the same tabulation will be performed for Grade 3 AEs. The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Dictionary for Adverse Event Terminology. The percentage of subjects with at least 1 report of unsolicited adverse event classified by the MedDRA, and reported up to 30 days after NTHi-Mcat vaccinations will be tabulated by group with exact 95% CI. The same tabulation will be performed for Grade 3 unsolicited adverse events, for unsolicited adverse events with a causal relationship to vaccination and for Grade 3 AEs causally related to vaccination. The number of subjects who experienced any serious adverse event (SAE) or any potential immune-mediated disease (pIMD) from Day 1 to Day 331 and from Day 331 to Day 661 will be reported. The number of subjects who experienced any AE leading to study withdrawal, from first vaccination up to study conclusion, or any SAE related to study participation or concurrent GSK medication/vaccination, during the entire study period, will be reported. A summary of subjects reporting concomitant medication/product will be provided.

10.3.6. Other analyses

Not applicable.

10.3.7. Interim analyses

No interim analysis is planned for this study. Data up to and including Day 331 are considered ‘final’ and completed data, while the remaining safety data are considered long-term safety follow-up.

10.4. Sequence of analyses

The integrated clinical study report will contain at least the final analyses of all primary and secondary endpoints. If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These analyses will be documented in annex(es) to the study report.

The analyses will be performed stepwise:

- A final analysis of immunogenicity, safety and reactogenicity for all subjects up to and including Day 331 ('Epoch 001') will be performed in a first step.

  A complete study report containing all data of 'Epoch 001' will be written and made available to the investigators at this stage.

- Analysis conducted on the data collected for all subjects from Day 331 up to and including Day 661 ('Epoch 002') will be performed in a second step.

  An integrated study report containing all data from Epoch 001 and Epoch 002 will be written and made available to the investigators.

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12. APPENDICES

12.1. Appendix 1: Abbreviations, glossary of terms and trademarks

12.1.1. List of abbreviations

(Amended 18 May 2020)

AE:	adverse event
AECOPD:	acute exacerbation of chronic obstructive pulmonary disease
AS01:	adjuvant system 01
C:	Call
CDC:	Centers for Disease Control
CI:	confidence interval
CLS:	Clinical Laboratory Sciences
CMI:	cell-mediated immune
CoP:	Correlate of Protection
COPD:	chronic obstructive pulmonary disease
COVID-19	***Coronavirus Disease 2019***
CP:	concept protocol
eCRF:	electronic Case Report Form
eTDF:	Electronic Temperature excursion Decision Form
D:	Day
ELISA:	enzyme-linked immunosorbent assay
EoS:	End of Study
EU/mL:	ELISA unit per millilitre
FDA:	Food and Drug Administration, United States of America
FEV1:	forced expiratory volume in 1 second

FVC:	forced vital capacity
GCP:	Good Clinical Practice
GMC	Geometric Mean Concentration
gE:	glycoprotein E
GMC:	geometric mean concentration
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
GSK:	GlaxoSmithKline
HZ:	herpes zoster
HZ/su:	herpes zoster subunit
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
IEC:	Independent Ethics Committee
Ig:	immunoglobulin
IM:	intramuscular
IMP:	Investigational Medicinal Product
IDMC:	Independent Data Monitoring Committee
IND:	Investigational New Drug
IRB:	Institutional Review Board
iSRC:	Internal Safety Review Committee
LLOQ:	lower limit of quantification
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
Mcat:	*Moraxella catarrhalis*
MedDRA:	Medical Dictionary for Regulatory Activities

MPL:	3-O-desacyl-4'-Monophosphoryl Lipid A
NI:	non-inferiority
NTHi:	non-typeable *Haemophilus influenzae*
PBMC:	peripheral blood mononuclear cells
PCD:	Primary Completion Date
PD:	protein D
PE:	protein E
PilA:	type IV pili subunit
pIMD:	potential immune-mediated disease
PP:	per protocol
PRO:	patient related outcomes
QS21:	Quillaja saponaria Molina, fraction 21 (Antigenics, New York, NY, US)
SAE:	Serious Adverse Event
SBIR:	System Built for Randomization
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
UspA2:	ubiquitous surface protein A2
V:	Visit
vacc:	vaccination
VZV:	varicella zoster virus

12.1.2. 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 1 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.

Certified copy: A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Current smoker:	A person who is currently smoking or who has stopped smoking within 6 months before study start.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the End of Study is defined as follows: last subject last visit (Day 661).
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardized term to replace: period, cycle, phase, stage.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
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 Section 10.2 for details on criteria for evaluability).
Former smoker:	A person who stopped smoking for at least 6 months at the time of study start.
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.

Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization 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.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Pack-years of smoking:	Pack-years is a quantification of cigarette smoking, a way to measure the total amount a person has smoked in the course of his/ her lifetime. The number of pack-years is calculated as follows: (average number of *cigarettes* smoked per day x number of years smoked)/ 20 E.g. a smoking history of 10 pack-years means having smoked 20 cigarettes per day for 10 years, or having smoked 10 cigarettes per day for 20 years. *Note*: For the purpose of this study, pipe and/or cigar use (including cigarillos) should not be used to calculate pack-year history.
Pharmacogenomics	The International Council on Harmonisation (ICH) E15 Guidance for Industry defines pharmacogenomics as Study of variation of DNA and RNA characteristics as related to drug or treatment response. Pharmacogenetics, which is a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety,

	efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research are not pharmacogenomics.
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.
Randomization:	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 1 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.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

12.1.3. Trademarks

Trademark Information

Trademarks of the GSK group of companies	Generic description
Shingrix	GlaxoSmithKline Biologicals' herpes zoster vaccine (recombinant, adjuvanted)
Adjupanrix	GlaxoSmithKline Biologicals' pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)
Prepandrix	GlaxoSmithKline Biologicals' prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)
Fendrix	GlaxoSmithKline Biologicals' hepatitis B (rDNA) vaccine (adjuvanted, adsorbed)
Cervarix	GlaxoSmithKline Biologicals' Human Papillomavirus vaccine (Types 16, 18) (Recombinant, adjuvanted, adsorbed)

Trademarks not owned by the GSK group of companies	Generic description
FluAd (Seqirus UK Ltd)	Influenza vaccine, adjuvanted
Chiromas (Seqirus, Inc) (Spain)	Influenza vaccine, adjuvanted
Gripguard (Seqirus, Inc) (France)	Influenza vaccine, adjuvanted

12.2. Appendix 2: Clinical laboratory tests

12.2.1. Laboratory assays: immune response

12.2.1.1. Humoral immunity

Serological assays will be performed at GSK Biologicals' laboratory or in a GSK designated laboratory using assays as described below and in Section 8.4.3. 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.

12.2.1.2. Cell-mediated immunity

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

12.3. Appendix 3: Clinical laboratories

Table 19 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 Clinical Laboratory Sciences, Marburg, Germany	Emil-von-Behring-Str. 76 35041 Marburg Germany

Table 20 Outsourced laboratories

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

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF) or Informed Assent Form (IAF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.4.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest prior initiation of the centre and at the end of the study. Investigators are responsible for providing an update of Financial Disclosure if their financial interest changes at any point during their participation in a study and for 1 year after completion of the study.

12.4.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary.

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

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the subject.

Subjects who are rescreened are required to sign a new ICF.

12.4.4. Data protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.4.5. Committees structure

No additional information.

12.4.6. Publication policy

GSK aims to publish the results of this study in searchable, peer reviewed scientific literature. GSK will target to submit within 18 months from LSLV for interventional

studies and from the completion of the analysis for non-interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

12.4.7. Dissemination of clinical study data

The key design elements of this protocol will be posted on the GSK Clinical Study Register and on publicly accessible registers including ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases (e.g. EudraCT database) in compliance with the applicable regulations.

GSK also assures that results will be submitted to ClinicalTrials.gov within the required time-frame, in compliance with the current regulations mentioned in the table below.

At the time of study results posting, the full study protocol and statistical analysis plan will also be posted on ClinicalTrials.gov.

In addition, for studies that are in scope of the EU Clinical Trial Regulation, summaries of the results of GSK interventional studies (phase I-IV) in adult population will be posted within defined timelines on the publicly EU Clinical Trial Register.

If it is not possible to submit a summary of the results within the required timelines in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

	Clinicaltrial.gov	EU
Protocol summary	Before enrolment of subjects	As per CTA submission/Before enrolment of subjects
Results summary	Within 12 months of PCD (Primary and safety endpoint results)/Within 12 months of LSLV* (for secondary endpoint results)	Within 6 months (for paediatric population studies)/Within 12 months (for adult population studies) of EoS*.

* As defined in the study protocol.

Under the framework of the SHARE initiative, anonymized patient-level data from GSK sponsored interventional studies that evaluate products will be made available within 6 months of this publication to independent researchers whose research proposals have been approved by an independent panel. Requests for access may be made through www.clinicalstudydatarequest.com.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12.4.8. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial may be added or reduced where justified (in advance of trial initiation) based on the importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfil the requirements for certified copies.

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail). Safety and rights of subjects must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.4.9. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and source documents can be found in the Glossary of terms.

12.4.10. Study and site closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

The investigator will:

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

12.5. Appendix 5: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

12.5.1. Definition of AE

12.5.1.1. AE Definition

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

NOTE: 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 study treatment.

12.5.1.2. Events Meeting the AE Definition

Significant or unexpected worsening or exacerbation of the condition/indication under study.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine administration.
- 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).
- Medically attended visits related to adverse events (e.g. Hospital stays, physician visits and emergency room visits).

AEs to be recorded as endpoints (solicited AEs) are described in Section 12.5.3. All other AEs will be recorded as UNSOLICITED AEs.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

12.5.1.3. Events NOT Meeting the AE Definition

- 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 vaccination. These events will be recorded in the medical history section of the eCRF.

12.5.2. Definition of SAE

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 hospitalization,

   Note: In general, hospitalization 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 hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.

   Hospitalization 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 hospitalization but may jeopardize 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 hospitalization.

12.5.3. Solicited adverse events

Solicited local and general AEs occurring during a 7-day follow-up period after each NTHi-Mcat vaccination (i.e. the day of vaccination and the 6 subsequent days) and unsolicited AEs occurring during a 30-day follow-up period after each NTHi-Mcat vaccination (i.e. the day of vaccination and the 29 subsequent days), will be reported via diary cards. In addition, subjects will be asked at Phone contacts if there were any safety concerns in the last 7 days; this information will be recorded via the appropriate section of the eCRF.

a. Solicited local (injection-site) adverse events

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

Table 21 Solicited local adverse events

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

b. Solicited general adverse events

The following general AEs will be solicited:

Table 22 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms†
Headache
Myalgia
Chills

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

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

12.5.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalisation, or emergency room visit, or visit to/by a health care provider), or were of concern to the subject. In case of such events, subjects will be instructed to

contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects will be collected during interview with the subject and by review of available medical records at the next visit.

12.5.5. Adverse events of special interest (AESIs)

12.5.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AESIs 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 the Table 23(refer to Section 12.5.9.2).

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin and should also be recorded as a pIMD.

Table 23 List of potential immune-mediated diseases (pIMDs)

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

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

12.5.5.2. Other adverse events of special interest

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

12.5.6. 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 (e.g. in consultation with a physician) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 12.5.1 and 12.5.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

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

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

12.5.7.1. Pregnancy

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

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

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

The following should always be considered as SAE and will be reported as described in Sections 12.5.9.1 and 12.5.9.4:

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

  Note: the 22 weeks' cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognised that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine will be reported to GSK Biologicals as described in Section 12.5.9. While the investigator is not obligated to actively seek this information from former subjects, he/she may learn of a pregnancy through spontaneous reporting.

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

A pDiary, hereafter referred to as Subject Diary will be used in this study to capture solicited and unsolicited adverse events. The subject should be trained on how and when to complete each field of the Subject Diary.

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

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit when Subject Diary is dispensed. This training must be documented in the subject's source record.

At each NTHi-Mcat vaccination visit, diary cards will be provided to the subject. The subject will be instructed to measure and record the axillary body temperature, and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 29 days occurring after vaccination. The subject will be instructed to return the completed diary card to the investigator at the next study visit.

- Collect and verify completed diary cards during discussion with the subject on Day 121; Day 181; Day 271 (Visit 4_1, Visit 4_3, Visit 4_6), and Day 181; Day 241; Day 331 (Visit 6_1, Visit 6_3, Visit 6_6) in the Sh_NTHi-Mcat groups and on Day 31 (Visit 2) and Day 91 (Visit 4) in the NTHi-Mcat group.
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure.

The investigator will transcribe the collected information into the eCRF in English.

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

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

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at the last study visit or phone contact for each subject. See Section 12.5.9 for instructions on reporting of SAEs.

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

SAEs that are related to the study vaccine will be collected and recorded from the time of the first receipt of study vaccine until the subject is discharged from the study.

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

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end at last study visit/phone contact. See section 12.5.9 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end at the last study visit/phone contact. See section 12.5.9.5 for instructions on reporting of pIMDs.

12.5.8.2. Evaluation of adverse events and serious adverse events

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

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

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

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

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

12.5.8.2.2. Assessment of adverse events

1. Assessment of intensity

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

Table 24 Intensity scales for solicited symptoms

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

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

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

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

Temperature will be scored at GSK Biologicals as follows:

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

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

The intensity should be assigned to 1 of the following categories:

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

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in Section 12.5.2.

2. Assessment of causality

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

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

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

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

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

YES : There is a reasonable possibility that the study vaccine contributed to the AE.

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

*Assessment of causality for non-serious AEs is requested for NTHi-Mcat study vaccine only while assessment of causality for SAEs is required for both *Shingrix* and NTHi Mcat study vaccines.

If an event meets the criteria to be determined as 'serious' (see Section 12.5.2), 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).

3. Assessment of outcomes

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

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

12.5.8.2.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if he/she received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

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

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

SAEs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a pIMD.

12.5.9.2. SAEs requiring expedited reporting 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.

12.5.9.3. 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.

12.5.9.4. Completion and transmission of pregnancy reports to GSK Biologicals

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

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

12.5.9.5. Reporting of pIMDs to GSK Biologicals

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows 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 12.5.9.3 for back-up system in case the electronic reporting system does not work.

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

When additional SAE, pregnancy, or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 17.

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

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

12.5.11.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 17).

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 study visit/phone contact of the subject.

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

12.5.11.1.2. 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, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- with other non-serious AEs, until resolution of the event or if the subject is lost to follow-up.

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

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

12.5.11.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

12.6. Appendix 6: Contraceptive guidance and collection of pregnancy information

12.6.1. Definitions

12.6.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

12.6.1.1.1. Women in the following categories are not considered WOCBP

- Premenarchal

Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

- Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

12.6.2. Contraception guidance

- Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 25.

Table 25 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject, *(The information on the male sterility can come from the site personnel's review of the subject's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 1 month after the last dose of study treatment

12.6.3. Collection of pregnancy information

12.6.3.1. Male subjects with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male subject's female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK

- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

12.6.3.2. Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in 12.5.9. While the investigator is not obligated to actively **seek this** information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be discontinued from study treatment and followed-up until the final outcome.

12.7. Appendix 7: Country-specific requirements

12.7.1. Requirements for Estonia

No country-specific requirements.

12.7.2. Requirements for Finland

No country-specific requirements.

12.7.3. Requirements for France

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

- Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the Informed Consent Form. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.
- According to French Public Health Code law (L.1121-16 and R.1121-16), the following people must be registered in National File ("Fichier National"):
  - Healthy volunteer;
  - Subjects if the aim of the study is not linked to their disease;
  - Subjects on request of the ethics committee regarding study risks and constraints.

  The following details will be described:
  - Reference of the study
  - Surname and first name
  - Date and place of birth
  - Gender
  - Dates of beginning and termination of the study
  - Exclusion period during which the subject cannot participate to another study (French Public Health Code law L.1121-12)
  - The total amount of compensation.

  The subjects' registration in national file ("Fichier National") should be documented in the source document - subject notes and monitored by the CRA.

- The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.
- A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study if authorised by the Ethics Committee).

  It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:

  – is either affiliated to or beneficiary of a social security category;

  – has got an authorisation by the Ethics Committee.

2. Concerning the "STATISTICAL CONSIDERATIONS AND DATA ANALYSES" and specially in the "SAMPLE SIZE ASSUMPTIONS"

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

3. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- In section "Regulatory and Ethical Considerations, including the Informed Consent Process"

  – Concerning **the process for informing the subject**, the following text is added:

  French Patient Informed Consent Form is a document which summarizes the main features of the study and allows collection of the subject written consent in triplicate. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee and the maintenance of confidentiality of the returned consent form by GlaxoSmithKline France.

  – **Concerning the management of the Patient Informed Consent Forms,** the following text is added:

  The first copy of the Patient Informed Consent Form is kept by the investigator. The second copy is kept by the Medical Direction of GlaxoSmithKline France and the last copy is given to the subject.

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

  – the study number,

  – the identification of the Centre: name of the principal investigator and centre number,

  – the number of informed consents,

  – the date,

  – and the principal investigator's signature.

Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.

- NOTIFICATION TO THE HOSPITAL DIRECTOR

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- INFORMATION TO THE HOSPITAL PHARMACIST

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

4. Concerning the "DATA MANAGEMENT" the following text is added:

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

- DEMOGRAPHIC DATA

  In accordance with the Data Protection French Law n° 78-17 of 6th January 1978 – article 8, the ethnic origin can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- TESTING OF BIOLOGICAL SAMPLES

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

5. SAE

- "TRANSMISSION OF THE SAE REPORTS":

(Amended 18 May 2020)

The notification of ***all*** serious adverse events ***and all serious adverse reactions*** is done promptly (and at the latest within 24 hours) by the investigator to GlaxoSmithKline as explained in Section 8.5.4 and Table 17 of 209538 (NTHI MCAT-009) study protocol. GlaxoSmithKline has a legal responsibility to promptly notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation and this is applicable for all the study sites where 209538 study is planned to be conducted. As sponsor of 209538 study, GlaxoSmithKline has in place processes meant to communicate any issue ***(including: suspicions of unexpected serious adverse reactions (SUSAR) occurring in France and outside the national territory, expected serious adverse reactions and serious adverse events occurring in France, new facts and urgent security measures)*** as soon as possible to the ANSM in order to safeguard the subjects enrolled in the clinical trials in accordance with the national reporting requirements in France ***(Article R1123-54 and Article R1123-46 of the French Public Health Code)***. This communication applies as soon as the sponsor has the following information:

- Suspected investigational product
- Patient/subject who presents with the effect/event
- Reporter
- Single identification number for the research/number of the protocol
- Causality assessment if applicable.

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

Département de Pharmacovigilance

Laboratoire GlaxoSmithKline

23, rue François Jacob

92 500 Rueil-Malmaison

Tel: PPD

Fax: PPD

PPD

6. Monitoring visits

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

7. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's electronic Case Report Form (eCRF) use here below:

The Health Institution and the Investigator undertake:

1. That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the electronic Case Report Form (eCRF) of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
2. That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
3. That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
4. To keep the IT Equipment and/or access codes in a safe and secure place and to authorize only the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
5. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
6. To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

8. CTR publication

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

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

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

12.7.4. Requirements for Italy

No country-specific requirements.

12.7.5. Requirements for Spain

No country-specific requirements.

12.8. Appendix 8: Protocol Amendment/Administrative change history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	18-MAY-2020
Administrative change 1	14-DEC-2018
Original Protocol	03-DEC-2018

Overall Rationale for the Administrative Change 1 14 December 2018

Section # and Name	Description of Change	Brief Rationale
Title page, Contributing authors	Inclusion of Study Delivery Lead in list of contributing authors	Inclusion of details for study delivery lead which were missing in the previous protocol
Section 12.7.3 Requirements for France	In this administrative change, the phrase "legally appointed representative (LAR)" was removed from Appendix 7 "Country-specific Requirements: France" and a typographical error was corrected (see below).	In this administrative change, the phrase "legally appointed representative (LAR)" was removed from Appendix 7 "Country-specific Requirements: France" in order that that the protocol was aligned with study documentation at a local level, and a typographical error was corrected for clarity

Detailed description of Protocol Administrative Change 1 14 December 2018 changes:

Table of contents, list of tables, list of figures and in-text cross references were updated following the protocol administrative changes.

In the list of contributing authors on the title page the study delivery lead was added to the list of contributors indicated using ***bold italic*** below:

- PPD ***(Study Delivery Lead)***

In Section 12.7.3 "Requirements for France" text was removed indicated using strikethrough formatting, below:

3. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- In section "Regulatory and Ethical Considerations, including the Informed Consent Process"
  - Concerning the process for informing the subject ~~and/or his/her legally authorized representative~~, the following text is added:

    French Patient Informed Consent Form is a document which summarizes the main features of the study and allows collection of the subject ~~and/or his/her legally authorized representative~~ written consent in triplicate. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee and

the maintenance of confidentiality of the returned consent form by GlaxoSmithKline France.

– Concerning the management of the Patient Informed Consent Forms, the following text is added:

The first copy of the Patient Informed Consent Form is kept by the investigator. The second copy is kept by the Medical Direction of GlaxoSmithKline France and the last copy(ies) is (are) given to the subject ~~and/or his/her legally authorized representative~~.

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

– the study number,

– the identification of the Centre: name of the principal investigator and centre number,

– the number of informed consents,

– the date,

– and the principal investigator's signature.

Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.

Overall Rationale for the Amendment 1 18 May 2020

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

The current analysis of the primary objective is planned on the per-protocol population. The use of the per protocol defined windows for vaccination and blood draws minimizes potential variability within the data for statistical comparisons. The planned analysis would test at least 1 geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. To control the type I error below 2.5% (one-sided), a sequential procedure -is planned in the protocol. Starting from the 6-months lag, the 3-months NI will be tested only if the 6-months NI will be demonstrated, while the 1-month NI will be tested only if the 6-months and 3-months NI will be both demonstrated. The expected sample size would allow to reach 80% of power.

The study started on 23 Apr 2019. At the time of writing, group Sh_NTHi-Mcat_**1** and control group NTHi-Mcat have completed the vaccination schedule and the blood draw as dictated by the study protocol, whereas the less advanced groups (Sh_NTHi-Mcat_**3** and Sh_NTHi-Mcat_**6**) are either due to receive the study vaccine or to undergo a blood draw. In accordance with the safety measures applied for COVID-19 containment in the Countries where the study is conducted, a number of study visits are unlikely to occur as

planned. This is expected to impact 2 of the study groups (Sh_NTHi-Mcat_**3** and Sh_NTHi-Mcat_**6**), for which the visits to collect data for primary endpoint are likely to occur while COVID-19 containment measures are in place.

This protocol amendment 1 includes a modified primary objective, should the Sh-NTHI-Mcat_6 **or** the Sh-NTHI-Mcat_**3** and Sh_NTHi-Mcat_**3** groups not meet the per-protocol defined sample size. To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio will be presented for any group not meeting the per protocol sample size using all available data. The descriptive analysis may be used to support the interval between *Shingrix* and NTHi-Mcat vaccines administration for the planned NTHi-Mcat Phase III studies.

This protocol amendment 1 also outlines measures (e.g. for safety monitoring) that may be applicable during special circumstances, like COVID-19 pandemic, in order to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity. However, if the study specific visit and procedures can be completed, then they should be completed according to the protocol, taking into account clinical judgment and local public health guidance to protect the safety of staff and subjects.

In addition, provisions relating to specific reporting of serious adverse events and serious adverse reactions, in accordance with Article R1123-54 and Article R1123-46 of the French Public Health Code, are incorporated into the "Requirements for France" Section of this Protocol Amendment, in order to fulfill the commitment taken with French Health Authority.

Amended text is indicated in ***bold italics*** in the body of the protocol.

Section # and Name	Description of Change	Brief Rationale
Cover page	To swap the identifiers "short title" and "Detailed Title".	Identifiers need to be corrected
Contributing authors	Addition of new team members	To reflect changes in the Team and contributions to the protocol amendment
Sponsor signature page	To change the identifier "short title" to "Detailed Title".	The detailed title is presented on this page and the identifier needs to be corrected.
Investigator signature page	To change the identifier "short title" to "Detailed Title".	The detailed title is presented on this page and the identifier needs to be corrected.
Section 1 Synopsis; Objectives and endpoints	Modification of the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached, including addition of footnote and update of subsequent footnote referencing.	To add a modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of

Section # and Name	Description of Change	Brief Rationale
		study visits are unlikely to occur as planned.
Section 2 Schedule of Activities (SoA) – Table 3 and Table 4	Addition of footnotes: • 11 to add information related to the diagnosis of COVID-19 per the WHO case definition and to clarify that routine study procedures and timeframes for reporting of AEs / SAEs should be followed; and, • 12 to add information regarding alternatives to study contacts due to special circumstances (e.g. COVID-19 pandemic)	To provide a reference to the WHO case definition for COVID-19, and to clarify that recording of AEs (unsolicited AEs or AEs leading to withdrawal) or SAEs should be aligned with routine procedures for the detection, reporting and recording of AEs or SAEs and timeframes set out in the protocol. And, to add information regarding alternatives to study contacts due to special circumstances (e.g. COVID-19 pandemic)
Section 4 Objective(s) and endpoint(s); Table 6 Objectives and endpoints	Modification of the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached, including addition of footnote and update of subsequent footnote referencing.	To add a modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned.
Section 7.5.2 Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses	Correction of typographical error	To correct a minor typographical error to improve readability
Section 8 Study assessments and procedures	Addition of a subsection (Section 8.1) outlining study procedures during special circumstances (e.g. COVID-19 pandemic). (Subsequent Level 2 and Level 3 heading numbering updated.)	To propose alternatives to reduce contacts due to special circumstances (e.g. COVID-19 pandemic): e.g. for safety follow up visits can be replaced by phone calls or virtual contacts, diary cards can be sent back by conventional mail, etc..
Section 8.4.2.1 Blood sampling for immunogenicity assessment / Table 10 and Table 11	Addition of a footnote to clarify study procedures in special circumstances	To highlight alternatives to reduce contacts due to special circumstances (e.g. COVID-19 pandemic): e.g. for safety follow up visits can be replaced by phone calls or virtual contacts, diary cards can be sent back by conventional mail, etc..
Section 8.4.3.1 Humoral antibody responses	Correction of typographical error	To correct a minor typographical error to improve readability
Section 8.4.4.1 Immunological read-outs Table 14	Addition of a footnote to clarify study procedures in special circumstances	To highlight alternatives to reduce contacts due to special circumstances (e.g. COVID-19 pandemic): e.g. for safety follow up visits can be replaced by phone calls or virtual contacts, diary cards

Section # and Name	Description of Change	Brief Rationale
		can be sent back by conventional mail, etc..
Section 8.5 Safety assessments	Addition of a sentence to clarify reference for case definition and recording of COVID-19 cases	To note that diagnosis of COVID-19 should be aligned with WHO case definition, and routine procedures as outlined in the study protocol for detection, recording and follow-up of AEs/SAEs should be followed
Section 8.5.2 Time period and frequency for collecting AE and serious adverse event (SAE) information (and Table 15 and Table 16)	Addition of footnotes to clarify reference for case definition and recording of COVID-19 cases	To note that diagnosis of COVID-19 should be aligned with WHO case definition, and routine procedures as outlined in the study protocol for detection, recording and follow-up of AEs/SAEs should be followed
Section 10.1.1 Hypotheses related to primary and secondary objectives	Modification of the hypotheses related to the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached.	To include the hypothesis related to the modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned. This is expected to impact 1 or 2 study groups depending on the ongoing viability of visits.
Section 10.1.2 Sample size calculation	Modification of the sample size calculation related to the primary objective in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. Figure 2 removed as linked only to the primary objective without modifications.	To include the sample size calculation related to the modified primary objective to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned. This is expected to impact 1 or 2 study groups depending on the ongoing viability of visits.
Section 10.3.4 Immunogenicity analyses	Modification of the primary objective and detail related to the statistical analyses to be applied in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached.	To include the planned immunogenicity analyses in case the per-protocol sample size for 1 (or more) of the 4 study groups is not reached. This is necessary because the current analysis of the primary objective is planned on the per-protocol population but, due to the containment measures for

Section # and Name	Description of Change	Brief Rationale
		COVID-19 applied in the countries where the study is conducted, a number of study visits are unlikely to occur as planned. This is expected to impact 1 or 2 study groups depending on the ongoing viability of visits.
Section 12.1.1 List of abbreviations	Addition of COVID-19 and definition	To include a new abbreviation and corresponding definition used in the protocol
Section 12.4.5 Committees Structure	Addition of "No additional information"	To complete an empty section
Section 12.7.3 Requirements for France	Addition of specific provisions relating to specific reporting of serious adverse events and serious adverse reactions in accordance with Article R1123-54 and Article R1123-46 of the French Public Health Code.	To fulfil a commitment with the French Health Authority (ANSM), whereby GSK agreed that the term "issue" included: • suspicions of unexpected serious adverse reactions (SUSAR) occurring in France and outside the national territory; • expected serious adverse reactions and serious adverse events occurring in France; • new facts and urgent security measures.

Detailed description of Protocol Amendment 1 changes:

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

Cover page (short title and title)

~~Short Title~~ Detailed Title A Phase IIA, open-label study to evaluate the immunogenicity and safety of sequential use of GSK's investigational vaccine GSK3277511A when administered to healthy smokers and ex-smokers aged 50 to 80 years following receipt of *Shingrix* vaccine.

Contributing authors

- PPD (Study Statistician***s***)
- PPD (Oversight Data Manager***s***)
- PPD (Clinical Trials Supply Manager***s***)

Protocol Amendment 1 Sponsor Signatory Approval

~~Short Title~~ Detailed Title A Phase IIA, open-label study to evaluate the immunogenicity and safety of sequential use of GSK's investigational vaccine GSK3277511A when

administered to healthy smokers and ex-smokers aged 50 to 80 years following receipt of *Shingrix* vaccine.

Protocol *Amendment 1* Investigator Agreement

~~Short Title~~ Detailed Title A Phase IIA, open-label study to evaluate the immunogenicity and safety of sequential use of GSK's investigational vaccine GSK3277511A when administered to healthy smokers and ex-smokers aged 50 to 80 years following receipt of *Shingrix* vaccine.

Section 1. Synopsis / Objectives and endpoints

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Confirmatory • To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone. *Criterion:* • Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.	• Humoral immune response – Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat groups (Day 181; Day 241; Day 331) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 group:[2]	
Confirmatory ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 months after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone.*** ***Criterion:*** • ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2***	***Humoral immune response*** – ***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_3 group (Day 241) and Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups:[3]	
• ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose***	***Humoral immune response***

Objectives	Endpoints
2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 month after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone. ***Criterion:*** ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.***	***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***
Secondary	
Descriptive • To describe the humoral immune response of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when administered alone.	• Humoral response – Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations and seropositivity in all subjects before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group).[1,2***4***]

[1] Given the different intervals between vaccines, the label for study visits or contacts varies between treatment groups. Please refer to the study design diagram.

[***2***] ***To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 group will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration***

[***3***] ***To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the GMC ratio of the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration***

[2***4***] Cut-off for seropositivity will be the lower limit of quantification (LLOQ) of the assay.

Section 2 Schedule of Activities (SoA)

Table 3 Schedule of Activities: Sh_NTHi-Mcat groups

		Epoch 001									Epoch 002		
Contact type and contact timepoint by study group	Sh_NTHi-Mcat_1	V1_1 D1	V2_1 D61	V3_1 D91	C1_1 D98	V4_1 D121	V5_1 D151	C2_1 D158	V6_1 D181	C3_1 D331	N/A	V7_1 D511	C4_1 D661
	Sh_NTHi-Mcat_3	V1_3 D1	V2_3 D61	V3_3 D151	C1_3 D158	V4_3 D181	V5_3[12] D211	C2_3 D218	V6_3[12] D241	C3_3 D331	C4_3 D391	V7_3[12] D571	C5_3 D661
	Sh_NTHi-Mcat_6	V1_6 D1	V2_6 D61	V3_6[12] D241	C1_6 D248	V4_6[12] D271	V5_6[12] D301	C2_6 D308	V6_6[12] D331	N/A	C3_6 D481	V7_6[12] D661	N/A
Sampling timepoint (vaccinations)		Sh1	Sh2	NM1			NM2						
Recording of unsolicited AEs[11]				●	●	●	●	●	●				
Recording of AEs leading to withdrawal[11]		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]
Recording of SAEs[11] and pregnancies		●	●	●	●	●	●	●	●	●[7]	●[8]	●	●[7]

[11]. If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (unsolicited AEs or AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 15

[12]. Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)

Table 4 Schedule of Activities: NTHi-Mcat group

Epoch	Epoch 001								Epoch 002	
Type of contact	V1	C1	V2	V3	C2	V4	C3	C4	V5	C5
Time points	D1	D8	D31	D61	D68	D91	D241	D331	D421[9]	D661
Sampling time points	NM 1			NM 2						
Recording of AEs leading to withdrawal[8]	●	●	●	●	●	●	●	●	●	●
Recording of SAEs[8] and pregnancies	●	●	●	●	●	●	●	●	●	●

[8]. If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 16

[9]. Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)

Section 4 Objectives and Endpoints

Table 6 Study objectives and endpoints

Objectives	Endpoints
Primary	
Confirmatory • To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone. *Criterion:* • Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.	• Humoral immune response – Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat groups (Day 181; Day 241; Day 331) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 group:[2]	
Confirmatory ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 months after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone.*** ***Criterion:*** • ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2***	***Humoral immune response*** – ***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_3 group (Day 241) and Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups:[2]	
• ***To demonstrate the non-inferiority (NI) of the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 month after Shingrix vaccine versus the humoral immune response 1 month after Dose 2 of GSK Biologicals' NTHi-Mcat investigational vaccine alone.*** ***Criterion:*** ***Lower limit (LL) of the 2-sided 95% confidence interval (CI) of the geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat/NTHi-Mcat) is above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.***	***Humoral immune response*** ***Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations 1 month after Dose 2 of NTHi-Mcat vaccine in the Sh_NTHi-Mcat_1 group (Day 181) compared to antibody concentrations 1 month after Dose 2 in the NTHi-Mcat group (Day 91).[1]***
Secondary	
Descriptive	• Humoral response

Objectives	Endpoints
• To describe the humoral immune response of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when administered alone.	– Anti-PD, anti-PE, anti-PilA and anti-UspA2 antibody concentrations and seropositivity in all subjects before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group).[1,~~2~~***4***]
Descriptive • To describe the cell mediated immune (CMI) response (CD4+ T-cells) of GSK Biologicals' NTHi-Mcat investigational vaccine when administered 1 or 3 or 6 months after *Shingrix* vaccine or when NTHi-Mcat is administered alone, in the CMI response sub-cohort.	• CMI response – NTHi-specific and Mcat-specific CMI responses as measured by flow cytometry ICS (frequency of specific CD4+ T-cells expressing at least 2 different markers among CD40 ligand (CD40L), interleukin (IL)-2, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α) upon in vitro stimulation) before Dose 1 (Day 91; Day 151; Day 241 in the Sh_NTHi-Mcat groups and Day 1 in the NTHi-Mcat group), and 1 month after Dose 2 of NTHi-Mcat vaccine (Day 181; Day 241; Day 331 in the Sh_NTHi-Mcat groups and Day 91 in the NTHi-Mcat group) in the CMI response sub-cohort.[1,~~3~~***5***]

[1] Given the different intervals between vaccines, the label for study visits or contacts varies between treatment groups. Please refer to the study design diagram.

[2] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the GMC ratio of the Sh_NTHi-Mcat_6 group will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

[3] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the GMC ratio of the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

[~~2~~***4***] Cut-off for seropositivity will be the lower limit of quantification (LLOQ) of the assay.

[~~3~~***5***] Refer to Section 5.3.1 for details regarding the CMI response sub-cohort.

Section 7.5.2 Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the starting 6 months prior to the first vaccine dose (see Sec***tion*** 6.2.2~~.~~) and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of ~~of~~ NTHi-Mcat vaccine). For corticosteroids, this will mean prednisone ≥5 mg/day (for adult subjects), or equivalent. Topical steroids are allowed.
- Any vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending at the second blood draw (i.e. approximately 1 month after the administration of the second dose of ~~of~~NTHi-Mcat vaccine),* with the exception of non-MF59 adjuvanted influenza vaccines and pneumococcal vaccines which may be administered ≥15 days preceding or following any study vaccine dose.

Section 8 Study assessments and procedures

8.1 Study procedures during special circumstances

Under special circumstances, modification of specific study procedures may be implemented:

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

- ***Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.***
- ***Diary cards may be transmitted from and to the site by electronic means and or conventional mail.***

Section 8.4.2.1 Blood sampling for immunogenicity assessments

Table 10 Blood sampling for humoral immunogenicity

Sample type	Quantity	Unit	Study group	Timepoint[1]	Subjects

[1]. Refer also to Schedule of Activities (Table 3 and Table 4), and Section 8.1 for information on study procedures during special circumstances

Table 11 Blood sampling for CMI

Sample type	Quantity	Unit	Study group	Timepoint[2]	Subjects

[2]. Refer also to Schedule of Activities (Table 3 and Table 4), and Section 8.1 for information on study procedures during special circumstances

Section 8.4.3.1 Humoral antibody responses

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

Section 8.4.4.1 Immunological read-outs

Table 14 Immunological read-outs

Blood sampling timepoint		Study group	No. subjects	Component
Type of contact and timepoint[3]	Sampling timepoint			

[3]. Refer also to Schedule of Activities (Table 3 and Table 4), and Section 8.1 for information on study procedures during special circumstances

Section 8.5 Safety assessment

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Diagnosis of COVID-19 should be made in accordance with the WHO case definition. Cases should be categorised as AEs (unsolicited or AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in Table 15 and Table 16.

Section 8.5.2 Time period and frequency for collecting AE and serious adverse event (SAE) information (Table 15 and Table 16)

Table 15 Reporting periods for collecting safety information: Sh_NTHi-Mcat groups

Event	Study group	Contact type (V/C) and timepoint (D)											
	Sh_NTHi-Mcat_1	V1_1 D1	V2_1 D61	V3_1 D91	C1_1 D98	V4_1 D121	V5_1 D151	C2_1 D158	V6_1 D181	C3_1 D331	V7_1 D511	N/A	C4_1 D661
	Sh_NTHi-Mcat _3	V1_3 D1	V2_3 D61	V3_3 D151	C1_3 D158	V4_3 D181	V5_3** D211	C2_3 D218	V6_3** D241	C3_3 D331	C4_3 D391	V7_3** D571	C5_3 D661
	Sh_NTHi-Mcat _6	V1_6 D1	V2_6 D61	V3_6** D241	C1_6 D248	V4_6** D271	V5_6** D301	C2_6 D308	V6_6** D331	N/A	C3_6 D481	N/A	V7_6** D661
Unsolicited AEs*	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat _3 Sh_NTHi-Mcat _6												
AEs/SAEs leading to withdrawal from the study*	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat _3 Sh_NTHi-Mcat _6												
SAEs*	Sh_NTHi-Mcat_1 Sh_NTHi-Mcat _3 Sh_NTHi-Mcat _6												

AEs = adverse events; C = Call; D = Day; N/A = not applicable; pIMDs= potential immune mediated diseases; SAEs = serious adverse events; Sh = *Shingrix*; V = Visit

**** If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (unsolicited AEs, AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the defined time period***

***** Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)***

Table 16 Reporting periods for collecting safety information: NTHi-Mcat group

Event	Contact type (V/C) and timepoint (D)									
	V1 D1	C1 D8	V2 D31	V3 D61	C2 D68	V4 D91	C3 D241	C4 D331	V5** D421	C5 D661
AEs/SAEs leading to withdrawal from the study*										
SAEs*										
SAEs related to study participation or concurrent GSK medication/vaccine										
Pregnancies										
pIMDs										

AEs = adverse events; C = Call; D = Day; N/A = not applicable; pIMDs= potential immune mediated diseases; SAEs = serious adverse events; V = Visit

**** If a diagnosis of COVID-19 is made in accordance with the current WHO case definition, cases should be reported as AEs (AEs leading to withdrawal) or SAEs (refer to Section 12.5 for safety definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the defined time period***

***** Visit may be a telephone contact, or other means of virtual contact or home visit during special circumstances (refer to Section 8.1 for information on study procedures during special circumstances)***

Section 10.1.1 Hypotheses related to primary and secondary objectives

The global null hypothesis related to the primary objective of the study is that at least one geometric mean concentration (GMC) ratio (Sh_NTHi-Mcat over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. This must be rejected in favour of the alternative hypothesis that all 4 GMCs (anti-PD, anti-PE, anti-PilA, anti-UspA2) are non-inferior in at least one time-lag group.

As defined in the study criteria of success, non-inferiority (NI) will be claimed for a specific time-lag if the lower limit of the 2-sided 95% CI of the GMC ratio (Sh_NTHi-Mcat_**k** over NTHi-Mcat, where **k**= [6, 3, 1]) will be above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA and anti-UspA2 concentration. Family-wise type I error is fixed at 2.5% (1-sided).

If the per-protocol sample size is either not reached in the Sh_NTHi-Mcat_6 group or not reached in the Sh_NTHi-Mcat_6 and in Sh_NTHi-Mcat_3 groups due to COVID-19 containment measures, a modification to the primary objective will be applied as follows:

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 due to COVID-19 containment measures:***

  The global null hypothesis related to the primary objective of the study is that at least 1 GMC ratio (Sh_NTHi-Mcat_k, where k=3 or 1 over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. This must be rejected in favour of the alternative hypothesis that all 4 GMCs (anti-PD, anti-PE, anti-PilA, anti-UspA2) are non-inferior in at least one time-lag group.

  As defined in the study criteria of success, non-inferiority (NI) will be claimed for a specific time-lag if the lower limit of the 2-sided 95% CI of the GMC ratio (Sh_NTHi-Mcat_k over NTHi-Mcat, where k= [3, 1]) will be above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA and anti-UspA2 concentration. Family-wise type I error is fixed at 2.5% (1-sided).

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 and Sh_NTHI-Mcat_3 due to COVID-19 containment measures:***

  The global null hypothesis related to the primary objective of the study is that the GMC ratio (Sh_NTHi-Mcat_1 over NTHi-Mcat) among anti-PD, anti-PE, anti-PilA, anti-UspA2 is inferior or equal to 0.667 in all time-lags under investigation at 1 month post-Dose 2 of NTHi-Mcat vaccine. This must be rejected in favour of the alternative hypothesis that all 4 GMCs (anti-PD, anti-PE, anti-PilA, anti-UspA2) are non-inferior.

  As defined in the study criteria of success, non-inferiority (NI) will if the lower limit of the 2-sided 95% CI of the GMC ratio (Sh_NTHi-Mcat_1 over NTHi-Mcat) will be above a limit of 0.667 for all anti-PD, anti-PE, anti-PilA and anti-UspA2 concentration. Family-wise type I error is fixed at 2.5% (1-sided).

Section 10.1.2 Sample size calculation

The study sample size is defined in order to ensure a global 80% power to conclude NI on all anti-PD, anti-PE, anti-PilA and anti-UspA2 for at least one time-lag. The target response-wise power is then 94.6%, assuming independence, for the 4 antigens response. The sample size calculation is based on a standard deviation of antibody $\log_{10}$-concentrations of 0.36 (based on NTHI MCAT-001) and a null true difference on the $\log_{10}$ scale.

To control the type I error below 2.5% (one-sided), a sequential procedure will be used for the primary objective. Starting from the 6-months lag, the 3-months NI will be tested only if the 6-months NI will be demonstrated, while the 1-month NI will be tested only if the 6-months and 3-months NI will be both demonstrated. Sequential testing procedure ensures also 80% power to conclude NI for each time-lag (i.e. conditionally on demonstrating NI at previous steps of the procedure). The power to prove all NI hypotheses is 51% (assuming independence).

The target sample size is 432 subjects evaluable for immunogenicity (108 subjects per study group). 'Evaluable subjects' means all subjects included in the set for the primary statistical analysis defined in Section 10.2. Considering that approximately 20% of the randomized subjects might withdraw, not be evaluable for immunogenicity or be excluded due to protocol deviations, the target sample size to be randomized is 540 subjects (135 subjects per study group).

~~Figure 2 Sequence for evaluating the primary objective in order to control the overall type I error below 2.5% (one-sided)~~

If the per-protocol sample size is either not reached in the Sh_NTHi-Mcat_6 group or not reached in the Sh_NTHi-Mcat_6 and in Sh_NTHi-Mcat_3 groups due to COVID-19 containment measures, a modification to the primary objective will be applied as follows:

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 due to COVID-19 containment measures:***

  To control the type I error below 2.5% (one-sided), a sequential procedure will be used for the primary objective. Starting from the 3-months lag, while the 1-month NI will be tested only if the 3-months NI will be demonstrated. Sequential testing procedure ensures also 80% power to conclude NI for each time-lag (i.e. conditionally on demonstrating NI at previous steps of the procedure). The power to prove all NI hypotheses is 64% (assuming independence).

- ***Per protocol sample size is not reached in group Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 due to COVID-19 containment measures:***

  The power to prove the NI hypothesis is 80%.

Section 10.3.4 Immunogenicity analyses

Endpoint	Statistical analysis methods
	Primary Endpoint(s)
Primary	**Between group assessment** Considering the sampling timepoint at 1 month after Dose 2 of NTHi-Mcat vaccine, the 2-sided 95% CIs for the group GMC ratio (Sh_NTHi-Mcat_1; _3; _6 group over NTHi-Mcat group) of anti-PD, anti-PE, anti-PilA, anti-UspA2 will be computed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations. The ANCOVA model will include study group, smoking status (current or former), age category (50–59, 60–69, 70–80 years of age) and centre as factors and the antibody concentration before Dose 1 as covariate. Non-inferiority for a specific time-lag will be claimed if the lower limit of the 2-sided 95% CI for the GMC ratio will be above 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2. The sequential procedure for multiple time-lags will be used: starting from the 6-months lag, the 3-months NI will be tested only if the 6-months NI will be demonstrated, while the 1-month NI will be tested only if the 6-months and 3-months NI will be both demonstrated.
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 group:[1]	***Considering the sampling timepoint at 1 month after Dose 2 of NTHi-Mcat vaccine, the 2-sided 95% CIs for the group GMC ratio (Sh_NTHi-Mcat_1; _3 group over NTHi-Mcat group) of anti-PD, anti-PE, anti-PilA, anti-UspA2 will be computed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations. The ANCOVA model will include study group, smoking status (current or former), age category (50–59, 60–69, 70–80 years of age) and centre as factors and the antibody concentration before Dose 1 as covariate.*** ***Non-inferiority for a specific time-lag will be claimed if the lower limit of the 2-sided 95% CI for the GMC ratio will be above 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2. The sequential procedure for multiple time-lags will be used: starting from the 3-months lag, the 1-month NI will be tested only if the 3-months NI will be demonstrated.***
The following modification of the primary objective will be applicable if the per-protocol set is not reached for the Sh_NTHi-Mcat_6 and the Sh_NTHi-Mcat_3 groups:[2]	***Considering the sampling timepoint at 1 month after Dose 2 of NTHi-Mcat vaccine, the 2-sided 95% CIs for the group GMC ratio (Sh_NTHi-Mcat_1 group over NTHi-Mcat group) of anti-PD, anti-PE, anti-PilA, anti-UspA2 will be computed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations. The ANCOVA model will include study group, smoking status (current or former), age category (50–59, 60–69, 70–80 years of age) and centre as factors and the antibody concentration before Dose 1 as covariate.*** ***Non-inferiority for a specific time-lag will be claimed if the lower limit of the 2-sided 95% CI for the GMC ratio will be above 0.667 for all anti-PD, anti-PE, anti-PilA, anti-UspA2.***
	Secondary Endpoint(s)

[1] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 group will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

[2] To complement this modified primary analysis, a descriptive analysis where the 95% confidence intervals around the geometric mean concentration (GMC) ratio of the Sh_NTHi-Mcat_6 and Sh_NTHi-Mcat_3 groups will be presented with all available data. The descriptive analysis may be used to support the interval between Shingrix and NTHi-Mcat vaccines administration

Section 12.1.1 List of abbreviations

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

Section 12.4.5 Committees Structure

No additional information

Section 12.7.3 Requirements for France

5. SAE

- "TRANSMISSION OF THE SAE REPORTS":

The notification of ~~the~~ ***all*** serious adverse events ***and all serious adverse reactions*** is done promptly (and at the latest within 24 hours) by the investigator to GlaxoSmithKline as explained in Section 8.4.4 and Table 17 of 209538 (NTHI MCAT-009) study protocol. GlaxoSmithKline has a legal responsibility to promptly notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation and this is applicable for all the study sites where 209538 study is planned to be conducted. As sponsor of 209538 study, GlaxoSmithKline has in place processes meant to communicate any issue ***(including: suspicions of unexpected serious adverse reactions (SUSAR) occurring in France and outside the national territory, expected serious adverse reactions and serious adverse events occurring in France, new facts and urgent security measures)*** as soon as possible to the ANSM in order to safeguard the subjects enrolled in the clinical trials in accordance with the national reporting requirements in France ***(Article R1123-54 and Article R1123-46 of the French Public Health Code)***. This communication applies as soon as the sponsor has the following information: