GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Immunogenicity and safety study of GSK's investigational vaccine (GSK3277511A) when administered in healthy smokers and ex-smokers following receipt of *Shingrix* vaccine.
eTrack study number and Abbreviated Title	209538 (NTHI MCAT-009)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Amendment 2 Final: 20 May 2020

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CMI	Cell-Mediated Immune
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
eTMF	Electronic Trial Master File
EU/mL	ELISA unit per milliliter
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMR	Geometric mean ratio
GSK	GlaxoSmithKline
LL	Lower Limit
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
NA	Not Applicable
NI	Non-Inferiority
PD	Protocol Deviation

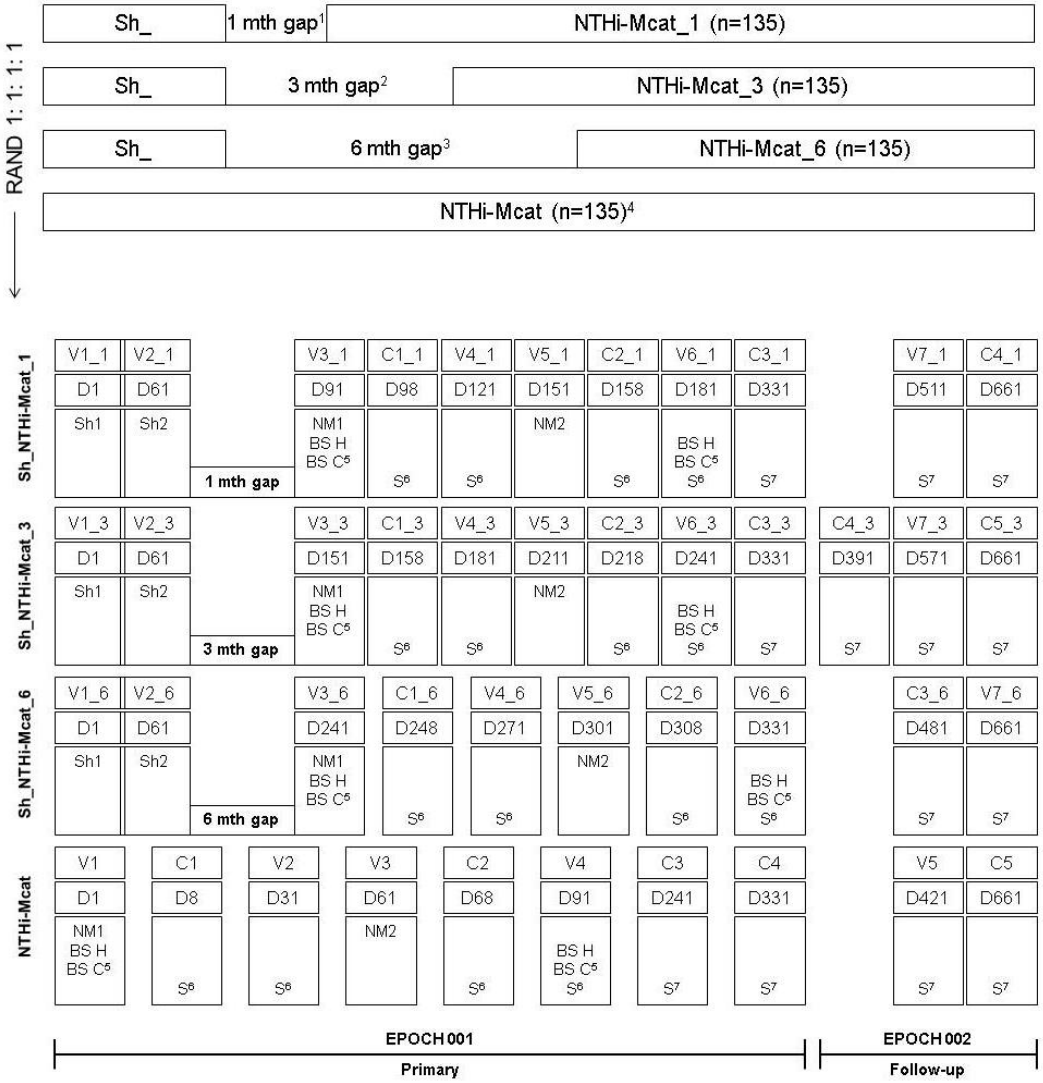
PPS	Per-Protocol Set
RCD	Reverse cumulative distribution
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
TFL	Tables Figures and Listings
ToC	Table of Content

1. DOCUMENT HISTORY

Date	Description	Protocol Version
01 APR 2019	First version	Protocol Administrative Change 1: 14 DEC 2018
30 JAN 2020	Amendment 1: • Section 5.3.2.1: update to the permutation test algorithm (recommendation from Center for Biologics Evaluation and Research)	Protocol Administrative Change 1: 14 DEC 2018
20 MAY 2020	Amendment 2: • Section 3: Objectives and endpoints • Section 4.2.4.1: Elimination codes from Per Protocol Set • Section 5.3.1: Analysis of immunogenicity planned per protocol • Section 5.3.2.1: Analysis of humoral response • Section 6: Analysis interpretation	Protocol Amendment 1: 18 MAY 2020

2. STUDY 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.] Patients 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 of the study protocol 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

- **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).
- **End of Study (EoS):** Last subject last visit (Day 661).
- **Study groups:** Approximately 540 eligible subjects who will be randomly assigned to 4 study groups in a (1: 1: 1: 1) ratio (Table 1). Please refer to Section 10.1 of the protocol for details related to the determination of sample size.

Table 1 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	●	●

- **Treatment allocation:** Subjects will be allocated to a study group using an automated, electronic System Built for Internet Randomization (SBIR). The randomization algorithm will use a minimization 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.
- **Blinding:** open-label.
- **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:** 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 7-day follow-up period after each NTHi-Mcat vaccination; 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, potential immune-mediated diseases (pIMDs), throughout the whole study period.

3. 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 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]***

Objectives	Endpoints
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]
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.[5]

Objectives	Endpoints
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.[5] • 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 and as such the Visit/contact label varies. Please refer to the study design diagram (Figure 1).
[2] 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] 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 of the study protocol for details regarding the CMI sub-cohort.

4. ANALYSIS SETS

4.1. Definition

Analysis Set	Description
Enrolled	All subjects who signed informed consent
Exposed (ES)	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 (FAS)	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 (PPS)	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[1] (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[1] (exposed set) who have solicited safety data

[1] Study treatment refers to the NTHi-Mcat vaccine. Please refer to Section 4.1.1 for additional details.

4.1.1. Additional considerations

The Enrolled set includes all subjects who signed informed consent, excluding subjects withdrawn prior to randomization (e.g. screening failures).

For the Unsolicited and Solicited safety sets, 1 dose of the study treatment refers to the administration of at least 1 dose of the NTHi-Mcat vaccine, in line with the study analysis of solicited and unsolicited AEs. In addition, subjects exposed to *Shingrix* only (if any) will be included in an extra group named “Shingrix only” for the safety analyses based on the Exposed Set (ES). Refer to Section 9.1.2 for more details about the algorithm to attribute subjects to groups for the purpose of safety analyses.

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) will be used for identifying subjects eliminated from the ES.

Subjects assigned to code 1030.b (not administering any NTHi-Mcat vaccine), but not to code 1030 will be identified as subjects belonging to the "Shingrix only" group.

4.2.2. Elimination from Full analysis set (FAS)

4.2.2.1. Excluded subjects

A subject will be excluded from the FAS analysis under the following conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
800	Fraudulent data	All	HUM, CMI
900	Invalid informed consent	All	HUM, CMI
1030	Study vaccine not administered at all	All	HUM, CMI
2100.a	Humoral immune response results not available post-vaccination	V6_1, V6_3, V6_6, V4	HUM
2100.b	CMI response results not available post-vaccination	V6_1, V6_3, V6_6, V4	CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.
Note: in case a subject is bled but blood sample is not planned per study protocol (code 2130), the unexpected sample is eliminated from the analysis, but subject is retained.

4.2.3. Elimination from Modified full analysis set (mFAS)

4.2.3.1. Excluded subjects

A subject will be excluded from the mFAS analysis if excluded from the FAS and under the following additional conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
1030.b	Not administering any NTHi-Mcat vaccine	All	HUM, CMI
1070.a	Incomplete treatment course	All	HUM, CMI
1070.a	Other deviations related to wrong treatment administered (including randomization failure)	All	HUM, CMI
2080	Subjects did not comply with Sh_NTHi-Mcat vaccination schedule	V3_1, V3_3, V3_6	HUM, CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.

4.2.4. Elimination from Per-protocol analysis set (PPS)

4.2.4.1. Excluded subjects

A subject will be excluded from the PPS analysis if excluded from the mFAS and under the following additional conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
1040	Administration of concomitant vaccine(s) forbidden in the protocol	All	HUM, CMI
1070	Vaccination not according to protocol	All	HUM, CMI
1080	Vaccine temperature deviation	All	HUM, CMI
1090	Expired vaccine administered	All	HUM, CMI
2010	Protocol violation (inclusion/exclusion criteria)	All	HUM, CMI
2040	Administration of any medication forbidden by the protocol	All	HUM, CMI
2050	Medical condition forbidden by the protocol	All	HUM, CMI
2080	Subjects did not comply with vaccination schedule	All	HUM, CMI
2090.a	Subjects did not comply with blood sample schedule (sample for humoral immune response)	All	HUM
2090.b	Subjects did not comply with blood sample schedule (sample for CMI response)	All	CMI
2100.a	Humoral immune response results not available	All	HUM
2100.b	CMI response results not available	All	CMI
2120.a	Obvious incoherence or abnormality or error in data (data on humoral immune response)	All	HUM
2120.b	Obvious incoherence or abnormality or error in data (data on CMI response)	All	CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort. In case of missed assessment or assessment not properly performed, the codes 2100c and 2120c can be applicable; decision is taken case by case.

4.2.5. Elimination from unsolicited and solicited safety set

4.2.5.1. Excluded subjects

4.2.5.1.1. Unsolicited safety set

Code 1030.b (not administering any NTHi-Mcat vaccine), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used to identify subjects eliminated from the unsolicited safety set.

Code 1150 will be attributed to subjects if all the following conditions are met: subject did not complete the safety assessment following the 7-day follow-up period after NTHi-Mcat vaccinations (i.e. phone contacts), did not return the pDiary, did not return for the scheduled visit 30-days after the NTHi-Mcat vaccinations and did not report any unsolicited AE.

Code 1070.a will be used to identify subjects eliminated from the Unsolicited Safety Set by visit when the NTHi-Mcat vaccination is not administered at that visit.

4.2.5.1.2. Solicited safety set

Code 1030.b (not administering any NTHi-Mcat vaccine), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used to identify subjects eliminated from the solicited safety set.

Code 1070.a will be used to identify subjects eliminated from the Solicited Safety Set by visit when the NTHi-Mcat vaccination is not administered at that visit.

5. STATISTICAL ANALYSES

Note that standard data derivation rules and statistical methods are described in "business rules document" and will not be repeated below. The study specific data derivation rules and statistical methods will be described in Section 9.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic characteristics (including age at first study vaccination in years, gender, race, ethnicity and smoking status) will be summarized by study group 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 PPS and mFAS will be tabulated.

5.1.2. Additional considerations

Summaries of demographic/baseline characteristics will include: age, country, centre, gender, race, ethnicity, smoking status, pack-years and vital signs (including body mass index [BMI]).

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

None.

5.2.2. Additional considerations

The number and percentage of subjects who received study vaccine doses will be tabulated for each study group (based on the ES).

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

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

Endpoint	Statistical analysis methods
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.

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 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 endpoints	
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).

Endpoint	Statistical analysis methods
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] 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] 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

5.3.2. Additional considerations

The supplementary analysis based on the mFAS will be performed if the percentage of mFAS subjects excluded from the PPS is more than 10%.

5.3.2.1. Analysis of humoral response

Hypothesis related to the primary objective

The global null hypothesis related to the primary objective of the study is that at least 1 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. Family-wise type I error is fixed at 2.5% (1-sided).

Geometric mean concentration and geometric mean concentration ratio

For each antigen and study group, at 1 month after Dose 2 of NTHi-Mcat vaccine, adjusted GMCs and GMCs ratios with corresponding 95% CIs will be obtained exponentiating (base 10) the least square means and the lower and upper limits of the 95% CIs derived from the ANCOVA model. The ANCOVA model will be implemented in SAS, similarly to the following code:

```
PROC GLM data=<dataset>;
BY antigen;
class group age smoking_status centre;
MODEL log(concentr)= group age smoking_status centre log(pre_concentr);
LSMEAN group / CL PDIFF ALPHA=0.05;
RUN;
```

Contrasts to be included: Sh_NTHi-Mcat_6 vs NTHi-Mcat, Sh_NTHi-Mcat_3 vs NTHi-Mcat, Sh_NTHi-Mcat_1 vs NTHi-Mcat.

In addition, unadjusted GMCs and GMRs will be presented for each timepoint (pre-Dose 1 and post-Dose 2 of NTHi-Mcat vaccine) with a descriptive purpose.

Permutation test (sensitivity analysis on primary objectives)

Based on the covariate-adaptive treatment assignment algorithm (see Section 10.3), the following permutation test will be performed as a sensitivity analysis on the primary objectives[1] [Wiens, 2006, Hasegawa, 2009 and Ernst, 2004] in the PPS.

For each antigen, let $\mathbf{X}=(X_1, \ldots, X_N)$ the logarithmically-transformed antibody concentrations for the NTHi-Mcat group and $\mathbf{Y_{1/3/6}}=(Y_1, \ldots, Y_N)$ the logarithmically-transformed antibody concentrations for one of the Sh_NTHi-Mcat groups at 1 month after Dose 2 of NTHi-Mcat vaccine, a non-inferiority permutation test can be obtained from a superiority permutation test on $\dot{\mathbf{X}}=(X_1, \ldots, X_N)$ against $\dot{\mathbf{Y}}_{\mathbf{1/3/6}}=(Y_1 + \delta, \ldots, Y_N + \delta)$ with $\delta = 0.176 = -\log_{10}(0.667)$.

The original treatment assignment algorithm will be used to re-randomize subjects while keeping antibody concentrations, covariates and entry order as observed. The procedure will be as follows:

1. Fit the ANCOVA model to obtain the test statistics $T^*_{1/3/6}$ for the superiority of $\dot{\mathbf{X}}$ against $\dot{\mathbf{Y}}_{\mathbf{1/3/6}}$.
2. Estimate the distribution of the test statistics with R=10000 repetitions of the following 2 steps:
   a. Re-randomize treatment assignment of all 4 groups (original algorithm).
   b. Re-fit the ANCOVA model to re-obtain the test statistics $T_{1/3/6}$.
3. Derive the permutation p-values associated to the observed test statistics (from step 1) based on the empirical distributions in Step 2

$\mathbf{p}_{1/3/6} = M+1/R+1$

Where M is the number of repetitions such that $T_{1/3/6} \geq T^*_{1/3/6}$.

[1] if the primary objective, following the assessment in term of number of subjects in PPS, is based on a reduce number of groups, the permutation p-values associated to the observed test statistics will be derived only for the groups participating to the primary objective.

Seropositivity rate and fold increase

For each antigen, timepoint and study group, the seropositivity rate (defined as the proportion of subjects with an antibody concentration greater or equal to the assay cut-off) with exact 95% CIs will be computed using the method referenced in section 10.1.5.1. Assay cut-offs are reported in section 9.1.1. In addition, percentages of subjects with a 2/4/8-fold increase will be presented with associated 95% CI.

Reverse cumulative distribution curves

Reverse cumulative distribution (RCD) curves for antibody concentrations will be plotted: the x-axis represents the antibody concentrations value (log-10 scale), while the y-axis the percentage of subjects having a log-transformed antibody value greater or equal to the corresponding x-value.

5.3.2.2. Analysis of CMI response

The frequency of **antigen-specific** CD4+ or CD8+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ or CD8+ T-cells producing at least 2 activation markers among CD40 Ligand (CD40L), IL-2, TNF- α, IFN- γ, IL-13 and IL-17, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ or CD8+ T-cells producing at least 2 activation markers upon in vitro stimulation in medium only (background condition). For descriptive statistics purposes, differences less or equal to zero (0) are imputed to 1.

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

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.

5.4.2. Additional considerations

5.4.2.1. Analysis of solicited AEs

The analysis of solicited AEs will be performed on the Solicited safety set.

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

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

Temperature (i.e. fever) will be scored at GSK Biologicals as follows:

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

Fever, defined as a body temperature of ≥37.5°C irrespective of route of measurement, will be integrated to the summaries as a general AE.

In addition, body temperature will be broken down into 0.5°C increments:

- <36.0
- 36.0 – 36.4
- 36.5 – 36.9
- 37.0 – 37.4
- 37.5 – 37.9
- 38.0 – 38.4
- 38.5 – 38.9
- 39.0 – 39.4
- 39.5 – 39.9
- ≥40.0

Compliance of subjects in completing solicited AEs information will be reported as the percentage of subjects completing at least 80% of the diary entries related to local and general solicited AEs.

5.4.2.2. Analysis of unsolicited AEs

The analysis of unsolicited AEs will be performed on the Unsolicited safety set.

Analysis of unsolicited AEs will be also stratified on AEs with a causal relationship to NTHi-Mcat vaccination.

5.4.2.3. Combined analysis of solicited and unsolicited AEs

The combined analysis of solicited and unsolicited AEs will be performed on the Unsolicited safety set.

Solicited AEs will be coded by MedDRA as per the following codes:

Solicited symptom	Preferred Term code	Corresponding Preferred Term decode
Pain	10022086	Injection site pain
Redness	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Myalgia	10028411	Myalgia
Chills	10008531	Chills
Fever	10037660	Pyrexia

Combined analysis of solicited and unsolicited AEs will be also stratified on AEs with a causal relationship to NTHi-Mcat vaccination (all solicited AEs are considered causally related).

5.4.2.4. Analysis of SAEs and pIMDs

The analysis of SAEs and pIMDs will be performed on the Exposed Set (ES).

Analysis of SAEs will include:

- All SAEs from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
- Fatal SAEs from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
- Related SAEs:
  - To any study vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
  - To the NTHi-Mcat vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661, from the day of the first NTHi-Mcat vaccination up to 1 month following the second dose, from the day of the first NTHi-Mcat vaccination up to 6 months following the second dose and from the day of the first NTHi-Mcat vaccination up to 12 months following the second dose (all groups except “Shingrix only”).
  - To *Shingrix* vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661 (all groups except NTHi-Mcat).

Analysis of pIMDs will include all occurrences from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.

5.4.2.5. Other safety analyses

Medications will be coded using GSKDRUG dictionary.

All collected concomitant medications and vaccinations will be listed. In addition, prior and concomitant vaccinations will be summarized. In case of pregnancies during the study, follow-up data and pregnancy outcomes will be described in detail.

6. ANALYSIS INTERPRETATION

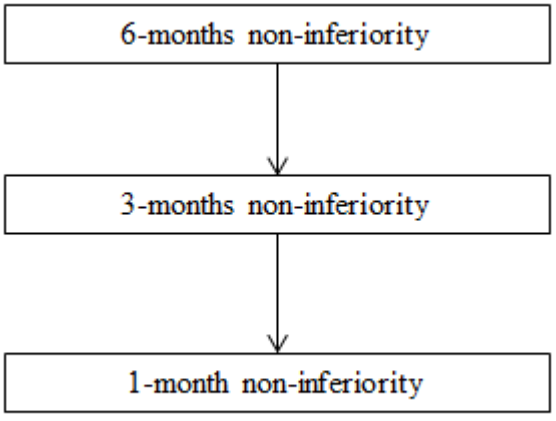
Except for analysis on primary objectives, with predefined success criteria and an appropriate type I error control, comparative analyses are descriptive with the aim to characterize the difference between groups.

With respect to confirmatory analyses on primary objectives the interpretation will be done in a hierarchical manner, except if only the group Sh_NTHi-Mcat_1 reached the number of subjects planned in the PPS, in this case we will have only one comparison to interpret.

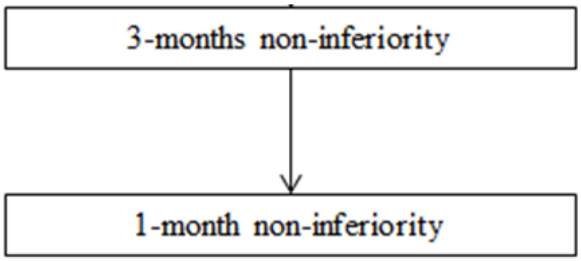
In case of sequential testing will be applied , each non inferiority can only be concluded if all the associated criteria are met and all previous non inferiority have been concluded (see Figure 2): starting from the 6-months lag, the 3-months NI can be achieved only if the 6-months NI is demonstrated, while the 1-month NI can be achieved only if the 6-months and 3-months NI are both demonstrated. Starting from the 3-months lag, the 1-month NI can be achieved only if the 3-months NI is demonstrated.

This sequential procedure enables to control the overall type I error below 2.5% (one-sided) [Dmitrienko, 2009].

Figure 2 Sequence for evaluating the primary objective in order to control the overall type I error below 2.5% (one-sided) in case all groups reached the number of subjects planned in the PPS



If the per-protocol sample size is not reached in the Sh_NTHi-Mcat_6 group, the sequential procedure enables to control the overall type I error below 2.5% (one-sided) [Dmitrienko, 2009] will be:



7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The integrated clinical study report (CSR) 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 CSR containing all data from Epoch 001 and Epoch 002 will be written and made available to the investigators.

Description	**Disclosure Purpose (CTRS=public posting, SR=study report, internal)**
Final Analysis Epoch 001	Web disclosure (CTRS), Study report (SR)
Analysis of Follow-up Epoch	Web disclosure (CTRS), Study report (SR)

7.2. Statistical considerations for 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.

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in Section 10.1

9.1. Data derivation

9.1.1. Assay cut-offs for serology results

Component	Method	Unit[1]	Assay cut-off[1]
anti-PD antibody	ELISA	EU/mL	153
anti-PE antibody	ELISA	EU/mL	25
anti-PilA antibody	ELISA	EU/mL	16
anti-UspA2 IgG antibody	ELISA	EU/mL	38

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.

9.1.2. Attributing subjects to time-lag groups

For the purpose of safety analyses, the following rule will be used to attribute exposed subjects to a specific group.

- If a subject receives no *Shingrix* vaccination → NTHi-Mcat group
- If a subject receives at least 1 *Shingrix* vaccination, but no NTHi-Mcat vaccination → "Shingrix only" group
- If a subject receives at least 1 *Shingrix* vaccination and at least 1 NTHi-Mcat vaccination, the difference, in days, between the latest Shingrix vaccination and the earliest NTHi-Mcat vaccination will be computed and converted in months (diff):
  - diff ≤ 2 → Sh_NTHi-Mcat_1 group
  - $2 <$ diff ≤ 4.5 → Sh_NTHi-Mcat_3 group
  - diff > 4.5 → Sh_NTHi-Mcat_6 group

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in Section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the eCRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.

- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited symptoms

10.1.2.3.1. Studies with paper diaries

Denominators for the summary of local (or general) solicited symptoms will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of local (or general) symptoms.

When a specific symptom is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the symptom in question), all daily measurements will be imputed as Grade 0.

When a specific symptom is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the symptom in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

When the occurrence of a specific symptom is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of symptoms (local or general) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

The following table shows how subjects contribute to each category for a specific solicited symptom over the Day X to Day Y post-vaccination period:

Solicited symptom category	Subjects included in the calculation of the numerator
Any	All subjects with at least one occurrence of the symptom at Grade 1, Grade 2, or Grade 3 between Day X and Day Y or with the symptom marked as present and at least one missing daily recording between Day X and Day Y
At least Grade 1	All subjects with at least one occurrence of the symptom at Grade 1, Grade 2, or Grade 3 between Day X and Day Y
At least Grade 2	All subjects with at least one occurrence of the symptom at Grade 2 or Grade 3 between Day X and Day Y
At least Grade 3	All subjects with at least one occurrence of the symptom at Grade 3 between Day X and Day Y

10.1.2.4. Unsolicited adverse events

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.2. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (weight in kilograms) / (height in meters)^2

10.1.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

10.1.3.4. Geometric mean concentrations (GMCs)

GMC calculations are performed by taking the inverse logarithm of the mean of the log-10 concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.5. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

10.1.3.6. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus 1 day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the consecutive days with the symptom reported at Grade 1 or higher. The duration of solicited events at a specific grade (e.g. Grade 3) will be calculated as the sum of the consecutive days with the symptom reported at that grade. The same rule applies for solicited events ongoing at the end of the solicited follow-up period considering the maximum intensity reported.

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered general events since the administration site flag is not included in the expedited adverse event eCRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarised, each event recorded as having occurred during a specific period will be counted as the number of occurrences the event is consecutively reported (at Grade 1 or higher). When the occurrences of solicited adverse events at a specific grade are summarised, each event recorded as having occurred at that grade during a specific period will be counted as the number of occurrences the event is consecutively reported at that grade.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with 1 more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with 1 decimal will be displayed with 2 decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, BMI, pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values below 10kg where 1 decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with 1 decimal.

10.1.4.4. Serological summary statistics

The number of decimals used when displaying GMCs and their confidence limits is shown in the following table:

GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the 1 with the higher number of decimals). For example, if GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Mietinnen and Nurminen [Miettinen, 1985].

10.1.5.3. Adjusted GMC ratios

When between-group GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

10.2. TFL ToC

The list of tables, figures and listings (TFL ToC) planned for this study can be found in eTMF folder section 11.1.1.

10.3. Randomization method and minimization algorithm

The minimization algorithm used at the GSK internet randomization system (i.e. SBIR) for study NTHI MCAT-009 is based on the following reference: "*White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978; 37: 849-857*" [White, 1978] and it is described below:

Notations

- K=3 input values [Centre, Smoking status and Age category] to be used for minimization, each with a weight w_k=1 (k=1,.., K) & l_k variants.
- I=4 treatment groups [NTHi-Mcat, Sh_NTHi-Mcat_6, Sh_NTHi-Mcat_3, Sh_NTHi-Mcat_1] with randomization ratio $a_1,\ldots,a_I$ [1:1:1:1]

Algorithm

For a new subject with input value variants $s_1 \ldots s_K$

Step 1: Minimization computation

Step 1.1: Initialize Problem flag to 0

For each input value variant s_k, compute the number of subjects already enrolled in each treatment group.

Let b_{ik} the number for treatment i & input value variant s_k: b_{ik} is the total number of subjects already randomized in treatment i and with variant s_k.

Step 1.2: For each treatment i: compute $A_i = 1/a_i * sum_k(w_k*b_{ik})$

Step 2: determine whether the algorithm is random or deterministic:

Generate R, a random number within [0-1], uniform distribution

Step 3: check determinism

If $R < 0.9$, go to step 4 (determinism) else go to step 5 (random)

Step 4: determinism

4.1: Identify all treatments with the lowest value A_i

4.2: Select randomly one of the treatments identified in step 4.1, let it be T.

Go to step 6, if no more treatment then randomization failed

Step 5: randomization

Select randomly one of the treatments, let it be T.

Go to step 6, if no more treatment then randomization failed.

Step 6: treatment allocation

Assign one of the treatment nr. related to treatment T in the subject's center.

If no treatment nr. related to treatment T is available in the subject's center, then go & repeat step 4 (determinism) or 5 (random) while dropping treatment T (set problem flag=1).

11. REFERENCES

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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Immunogenicity and safety study of GSK's investigational vaccine (GSK3277511A) when administered in healthy smokers and ex-smokers following receipt of *Shingrix* vaccine.
eTrack study number and Abbreviated Title	209538 (NTHI MCAT-009)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Amendment 1 Final: 30 January 2020

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CMI	Cell-Mediated Immune
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EU/mL	ELISA unit per milliliter
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
eTMF	Electronic Trial Master File
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMR	Geometric mean ratio
GSK	GlaxoSmithKline
LL	Lower Limit
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
NA	Not Applicable
NI	Non-Inferiority
PD	Protocol Deviation
PPS	Per-Protocol Set

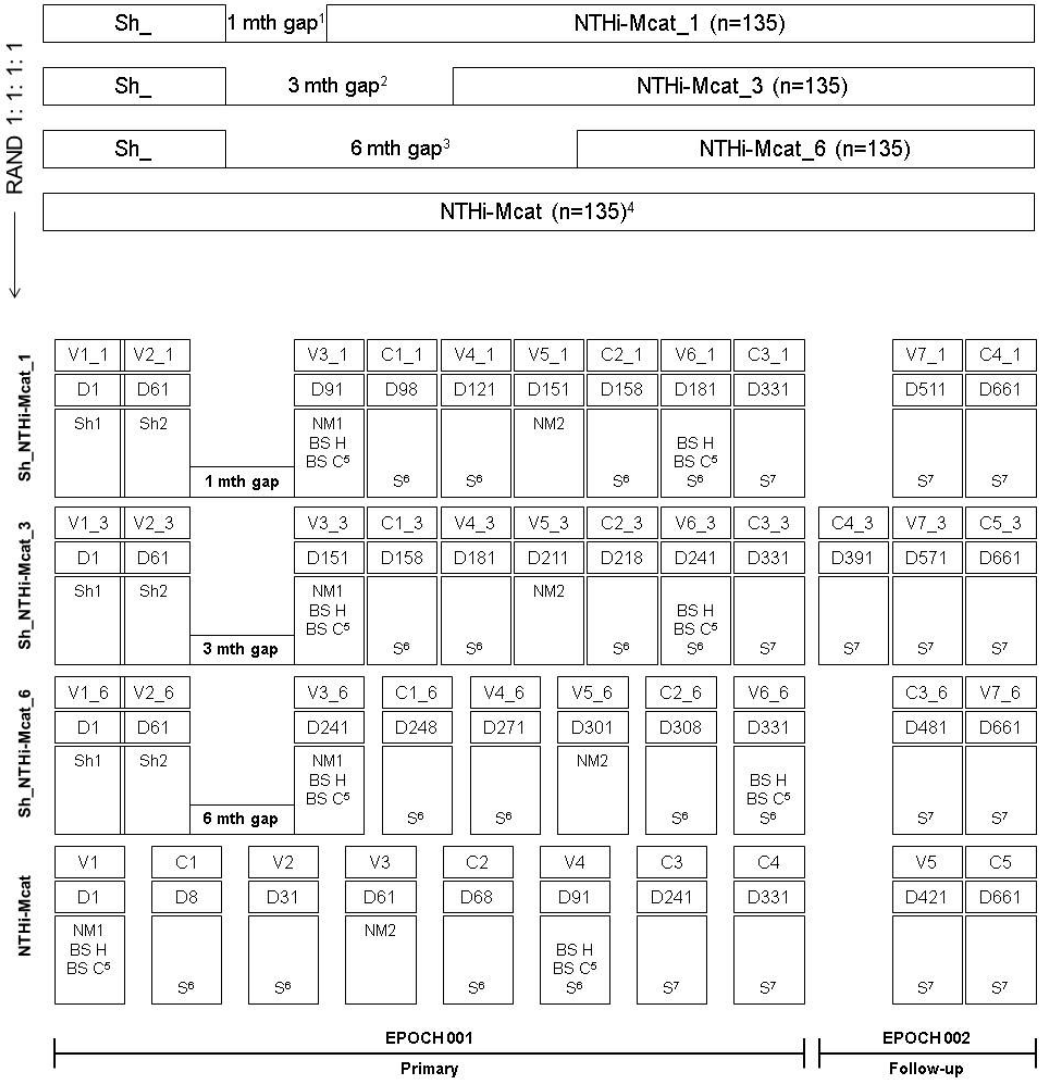
RCD	Reverse cumulative distribution
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
TFL	Tables Figures and Listings
ToC	Table of Content

1. DOCUMENT HISTORY

Date	Description	Protocol Version
01 APR 2019	First version	Protocol Administrative Change 1: 14 DEC 2018
30 JAN 2020	Amendment 1: • Section 5.3.2.1: update to the permutation test algorithm (recommendation from Center for Biologics Evaluation and Research)	Protocol Administrative Change 1: 14 DEC 2018

2. STUDY 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.] Patients 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 of the study protocol 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

- **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).
- **End of Study (EoS):** Last subject last visit (Day 661).
- **Study groups:** Approximately 540 eligible subjects who will be randomly assigned to 4 study groups in a (1: 1: 1: 1) ratio (Table 1). Please refer to Section 10.1 of the protocol for details related to the determination of sample size.

Table 1 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	●	●

- **Treatment allocation:** Subjects will be allocated to a study group using an automated, electronic System Built for Internet Randomization (SBIR). The randomization algorithm will use a minimization 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.
- **Blinding:** open-label.
- **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:** 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 7-day follow-up period after each NTHi-Mcat vaccination; 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, potential immune-mediated diseases (pIMDs), throughout the whole study period.

3. 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]
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.

Objectives	Endpoints
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]
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 and as such the Visit/contact label varies. Please refer to the study design diagram (Figure 1).
[2] Cut-off for seropositivity will be the lower limit of quantification (LLOQ) of the assay.
[3] Refer to Section 5.3.1 of the study protocol for details regarding the CMI sub-cohort.

4. ANALYSIS SETS

4.1. Definition

Analysis Set	Description
Enrolled	All subjects who signed informed consent
Exposed (ES)	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 (FAS)	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 (PPS)	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[1] (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[1] (exposed set) who have solicited safety data

[1] Study treatment refers to the NTHi-Mcat vaccine. Please refer to Section 4.1.1 for additional details.

4.1.1. Additional considerations

The Enrolled set includes all subjects who signed informed consent, excluding subjects withdrawn prior to randomization (e.g. screening failures).

For the Unsolicited and Solicited safety sets, 1 dose of the study treatment refers to the administration of at least 1 dose of the NTHi-Mcat vaccine, in line with the study analysis of solicited and unsolicited AEs. In addition, subjects exposed to *Shingrix* only (if any) will be included in an extra group named “Shingrix only” for the safety analyses based on the Exposed Set (ES). Refer to Section 9.1.2 for more details about the algorithm to attribute subjects to groups for the purpose of safety analyses.

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) will be used for identifying subjects eliminated from the ES.

Subjects assigned to code 1030.b (not administering any NTHi-Mcat vaccine), but not to code 1030 will be identified as subjects belonging to the "Shingrix only" group.

4.2.2. Elimination from Full analysis set (FAS)

4.2.2.1. Excluded subjects

A subject will be excluded from the FAS analysis under the following conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
800	Fraudulent data	All	HUM, CMI
900	Invalid informed consent	All	HUM, CMI
1030	Study vaccine not administered at all	All	HUM, CMI
2100.a	Humoral immune response results not available post-vaccination	V6_1, V6_3, V6_6, V4	HUM
2100.b	CMI response results not available post-vaccination	V6_1, V6_3, V6_6, V4	CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.
Note: in case a subject is bled but blood sample is not planned per study protocol (code 2130), the unexpected sample is eliminated from the analysis, but subject is retained.

4.2.3. Elimination from Modified full analysis set (mFAS)

4.2.3.1. Excluded subjects

A subject will be excluded from the mFAS analysis if excluded from the FAS and under the following additional conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
1030.b	Not administering any NTHi-Mcat vaccine	All	HUM, CMI
1070.a	Incomplete treatment course	All	HUM, CMI
1070.a	Other deviations related to wrong treatment administered (including randomization failure)	All	HUM, CMI
2080	Subjects did not comply with Sh_NTHi-Mcat vaccination schedule	V3_1, V3_3, V3_6	HUM, CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.

4.2.4. Elimination from Per-protocol analysis set (PPS)

4.2.4.1. Excluded subjects

A subject will be excluded from the PPS analysis if excluded from the mFAS and under the following additional conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
1040	Administration of concomitant vaccine(s) forbidden in the protocol	All	HUM, CMI
1070	Vaccination not according to protocol	All	HUM, CMI
1080	Vaccine temperature deviation	All	HUM, CMI
1090	Expired vaccine administered	All	HUM, CMI
2010	Protocol violation (inclusion/exclusion criteria)	All	HUM, CMI
2040	Administration of any medication forbidden by the protocol	All	HUM, CMI
2050	Medical condition forbidden by the protocol	All	HUM, CMI
2080	Subjects did not comply with vaccination schedule	All	HUM, CMI
2090.a	Subjects did not comply with blood sample schedule (sample for humoral immune response)	All	HUM
2090.b	Subjects did not comply with blood sample schedule (sample for CMI response)	All	CMI
2100.a	Humoral immune response results not available	All	HUM
2100.b	CMI response results not available	All	CMI
2120.a	Obvious incoherence or abnormality or error in data (data on humoral immune response)	All	HUM
2120.b	Obvious incoherence or abnormality or error in data (data on CMI response)	All	CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.

4.2.5. Elimination from unsolicited and solicited safety set

4.2.5.1. Excluded subjects

4.2.5.1.1. Unsolicited safety set

Code 1030.b (not administering any NTHi-Mcat vaccine), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used to identify subjects eliminated from the unsolicited safety set.

Code 1150 will be attributed to subjects if all the following conditions are met: subject did not complete the safety assessment following the 7-day follow-up period after NTHi-Mcat vaccinations (i.e. phone contacts), did not return the pDiary, did not return for the scheduled visit 30-days after the NTHi-Mcat vaccinations and did not report any unsolicited AE.

Code 1070.a will be used to identify subjects eliminated from the Unsolicited Safety Set by visit when the NTHi-Mcat vaccination is not administered at that visit.

4.2.5.1.2. Solicited safety set

Code 1030.b (not administering any NTHi-Mcat vaccine), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used to identify subjects eliminated from the solicited safety set.

Code 1070.a will be used to identify subjects eliminated from the Solicited Safety Set by visit when the NTHi-Mcat vaccination is not administered at that visit.

5. STATISTICAL ANALYSES

Note that standard data derivation rules and statistical methods are described in "business rules document" and will not be repeated below. The study specific data derivation rules and statistical methods will be described in Section 9.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic characteristics (including age at first study vaccination in years, gender, race, ethnicity and smoking status) will be summarized by study group 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 PPS and mFAS will be tabulated.

5.1.2. Additional considerations

Summaries of demographic/baseline characteristics will include: age, country, centre, gender, race, ethnicity, smoking status, pack-years and vital signs (including body mass index [BMI]).

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

None.

5.2.2. Additional considerations

The number and percentage of subjects who received study vaccine doses will be tabulated for each study group (based on the ES).

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

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

Endpoint	Statistical analysis methods
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.
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.

Endpoint	Statistical analysis methods
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).

5.3.2. Additional considerations

The supplementary analysis based on the mFAS will be performed if the percentage of mFAS subjects excluded from the PPS is more than 10%.

5.3.2.1. Analysis of humoral response

Hypothesis related to the primary objective

The global null hypothesis related to the primary objective of the study is that at least 1 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. Family-wise type I error is fixed at 2.5% (1-sided).

Geometric mean concentration and geometric mean concentration ratio

For each antigen and study group, at 1 month after Dose 2 of NTHi-Mcat vaccine, adjusted GMCs and GMCs ratios with corresponding 95% CIs will be obtained exponentiating (base 10) the least square means and the lower and upper limits of the 95% CIs derived from the ANCOVA model. The ANCOVA model will be implemented in SAS, similarly to the following code:

```
PROC GLM data=<dataset>;
BY antigen;
class group age smoking_status centre;
MODEL log(concentr)= group age smoking_status centre log(pre_concentr);
LSMEAN group / CL PDIFF ALPHA=0.05;
RUN;
```

Contrasts to be included: Sh_NTHi-Mcat_6 vs NTHi-Mcat, Sh_NTHi-Mcat_3 vs NTHi-Mcat, Sh_NTHi-Mcat_1 vs NTHi-Mcat.

In addition, unadjusted GMCs and GMRs will be presented for each timepoint (pre-Dose 1 and post-Dose 2 of NTHi-Mcat vaccine) with a descriptive purpose.

Permutation test (sensitivity analysis on primary objectives)

Based on the covariate-adaptive treatment assignment algorithm (see Section 10.3), the following permutation test will be performed as a sensitivity analysis on the primary objectives [Wiens, 2006, Hasegawa, 2009 and Ernst, 2004] in the PPS.

For each antigen, let $\mathbf{X}=(X_1, \ldots, X_N)$ the logarithmically-transformed antibody concentrations for the NTHi-Mcat group and $\mathbf{Y_{1/3/6}}=(Y_1, \ldots, Y_N)$ the logarithmically-transformed antibody concentrations for one of the Sh_NTHi-Mcat groups at 1 month after Dose 2 of NTHi-Mcat vaccine, a non-inferiority permutation test can be obtained from a superiority permutation test on $\dot{\mathbf{X}}=(X_1, \ldots, X_N)$ against $\dot{\mathbf{Y}}_{\mathbf{1/3/6}}=(Y_1 + \delta, \ldots, Y_N + \delta)$ with $\delta = 0.176 = -\log_{10}(0.667)$.

The original treatment assignment algorithm will be used to re-randomize subjects while keeping antibody concentrations, covariates and entry order as observed. The procedure will be as follows:

1. Fit the ANCOVA model to obtain the test statistics $T^*_{1/3/6}$ for the superiority of $\dot{\mathbf{X}}$ against $\dot{\mathbf{Y}}_{\mathbf{1/3/6}}$.
2. Estimate the distribution of the test statistics with R=10000 repetitions of the following 2 steps:
   a. Re-randomize treatment assignment of all 4 groups (original algorithm).
   b. Re-fit the ANCOVA model to re-obtain the test statistics $T_{1/3/6}$.
3. Derive the permutation p-values associated to the observed test statistics (from step 1) based on the empirical distributions in Step 2

$\mathbf{p}_{1/3/6} = M+1/R+1$

Where M is the number of repetitions such that $T_{1/3/6} \geq T^*_{1/3/6}$.

Seropositivity rate and fold increase

For each antigen, timepoint and study group, the seropositivity rate (defined as the proportion of subjects with an antibody concentration greater or equal to the assay cut-off) with exact 95% CIs will be computed using the method referenced in section 10.1.5.1. Assay cut-offs are reported in section 9.1.1. In addition, percentages of subjects with a 2/4/8-fold increase will be presented with associated 95% CI.

Reverse cumulative distribution curves

Reverse cumulative distribution (RCD) curves for antibody concentrations will be plotted: the x-axis represents the antibody concentrations value (log-10 scale), while the y-axis the percentage of subjects having a log-transformed antibody value greater or equal to the corresponding x-value.

5.3.2.2. Analysis of CMI response

The frequency of **antigen-specific** CD4+ or CD8+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ or CD8+ T-cells producing at least 2 activation markers among CD40 Ligand (CD40L), IL-2, TNF- α, IFN- γ, IL-13 and IL-17, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ or CD8+ T-cells producing at least 2 activation markers upon in vitro stimulation in medium only (background condition). For descriptive statistics purposes, differences less or equal to zero (0) are imputed to 1.

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

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)

Endpoint	Statistical analysis methods
	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.

5.4.2. Additional considerations

5.4.2.1. Analysis of solicited AEs

The analysis of solicited AEs will be performed on the Solicited safety set.

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

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

Temperature (i.e. fever) will be scored at GSK Biologicals as follows:

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

Fever, defined as a body temperature of ≥37.5°C irrespective of route of measurement, will be integrated to the summaries as a general AE.

In addition, body temperature will be broken down into 0.5°C increments:

- <36.0
- 36.0 – 36.4
- 36.5 – 36.9
- 37.0 – 37.4
- 37.5 – 37.9
- 38.0 – 38.4
- 38.5 – 38.9
- 39.0 – 39.4
- 39.5 – 39.9
- ≥40.0

Compliance of subjects in completing solicited AEs information will be reported as the percentage of subjects completing at least 80% of the diary entries related to local and general solicited AEs.

5.4.2.2. Analysis of unsolicited AEs

The analysis of unsolicited AEs will be performed on the Unsolicited safety set.

Analysis of unsolicited AEs will be also stratified on AEs with a causal relationship to NTHi-Mcat vaccination.

5.4.2.3. Combined analysis of solicited and unsolicited AEs

The combined analysis of solicited and unsolicited AEs will be performed on the Unsolicited safety set.

Solicited AEs will be coded by MedDRA as per the following codes:

Solicited symptom	Preferred Term code	Corresponding Preferred Term decode
Pain	10022086	Injection site pain
Redness	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Myalgia	10028411	Myalgia
Chills	10008531	Chills
Fever	10037660	Pyrexia

Combined analysis of solicited and unsolicited AEs will be also stratified on AEs with a causal relationship to NTHi-Mcat vaccination (all solicited AEs are considered causally related).

5.4.2.4. Analysis of SAEs and pIMDs

The analysis of SAEs and pIMDs will be performed on the Exposed Set (ES).

Analysis of SAEs will include:

- All SAEs from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
- Fatal SAEs from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
- Related SAEs:
  - To any study vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.

- To the NTHi-Mcat vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661, from the day of the first NTHi-Mcat vaccination up to 1 month following the second dose, from the day of the first NTHi-Mcat vaccination up to 6 months following the second dose and from the day of the first NTHi-Mcat vaccination up to 12 months following the second dose (all groups except "Shingrix only").
- To *Shingrix* vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661 (all groups except NTHi-Mcat).

Analysis of pIMDs will include all occurrences from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.

5.4.2.5. Other safety analyses

Medications will be coded using GSKDRUG dictionary.

All collected concomitant medications and vaccinations will be listed. In addition, prior and concomitant vaccinations will be summarized. In case of pregnancies during the study, follow-up data and pregnancy outcomes will be described in detail.

6. ANALYSIS INTERPRETATION

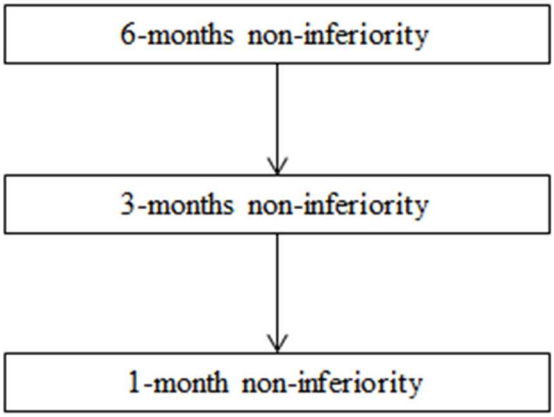
Except for analysis on primary objectives, with predefined success criteria and an appropriate type I error control, comparative analyses are descriptive with the aim to characterize the difference between groups.

With respect to confirmatory analyses on primary objectives the interpretation will be done in a hierarchical manner.

Each objective can only be reached if all the associated criteria are met and all previous objectives have been reached (see Figure 2): starting from the 6-months lag, the 3-months NI can be achieved only if the 6-months NI is demonstrated, while the 1-month NI can be achieved only if the 6-months and 3-months NI are both demonstrated.

This sequential procedure enables to control the overall type I error below 2.5% (one-sided) [Dmitrienko, 2009].

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



7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The integrated clinical study report (CSR) 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 CSR containing all data from Epoch 001 and Epoch 002 will be written and made available to the investigators.

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final Analysis Epoch 001	Web disclosure (CTRS), Study report (SR)
Analysis of Follow-up Epoch	Web disclosure (CTRS), Study report (SR)

7.2. Statistical considerations for 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.

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in Section 10.1

9.1. Data derivation

9.1.1. Assay cut-offs for serology results

Component	Method	Unit[1]	Assay cut-off[1]
anti-PD antibody	ELISA	EU/mL	153
anti-PE antibody	ELISA	EU/mL	25
anti-PilA antibody	ELISA	EU/mL	16
anti-UspA2 IgG antibody	ELISA	EU/mL	38

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.

9.1.2. Attributing subjects to time-lag groups

For the purpose of safety analyses, the following rule will be used to attribute exposed subjects to a specific group.

- If a subject receives no *Shingrix* vaccination → NTHi-Mcat group
- If a subject receives at least 1 *Shingrix* vaccination, but no NTHi-Mcat vaccination → "Shingrix only" group
- If a subject receives at least 1 *Shingrix* vaccination and at least 1 NTHi-Mcat vaccination, the difference, in days, between the latest Shingrix vaccination and the earliest NTHi-Mcat vaccination will be computed and converted in months (diff):
  - diff ≤ 2 → Sh_NTHi-Mcat_1 group
  - $2 <$ diff ≤ 4.5 → Sh_NTHi-Mcat_3 group
  - diff > 4.5 → Sh_NTHi-Mcat_6 group

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in Section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the eCRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.

- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited symptoms

10.1.2.3.1. Studies with paper diaries

Denominators for the summary of local (or general) solicited symptoms will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of local (or general) symptoms.

When a specific symptom is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the symptom in question), all daily measurements will be imputed as Grade 0.

When a specific symptom is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the symptom in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

When the occurrence of a specific symptom is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of symptoms (local or general) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

The following table shows how subjects contribute to each category for a specific solicited symptom over the Day X to Day Y post-vaccination period:

Solicited symptom category	Subjects included in the calculation of the numerator
Any	All subjects with at least one occurrence of the symptom at Grade 1, Grade 2, or Grade 3 between Day X and Day Y or with the symptom marked as present and at least one missing daily recording between Day X and Day Y
At least Grade 1	All subjects with at least one occurrence of the symptom at Grade 1, Grade 2, or Grade 3 between Day X and Day Y
At least Grade 2	All subjects with at least one occurrence of the symptom at Grade 2 or Grade 3 between Day X and Day Y
At least Grade 3	All subjects with at least one occurrence of the symptom at Grade 3 between Day X and Day Y

10.1.2.4. Unsolicited adverse events

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.2. Body mass index (BMI)

BMI will be calculated as follows:

$$\text{BMI} = (\text{weight in kilograms}) / (\text{height in meters})^2$$

10.1.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

10.1.3.4. Geometric mean concentrations (GMCs)

GMC calculations are performed by taking the inverse logarithm of the mean of the log-10 concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.5. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

10.1.3.6. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus 1 day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the consecutive days with the symptom reported at Grade 1 or higher. The duration of solicited events at a specific grade (e.g. Grade 3) will be calculated as the sum of the consecutive days with the symptom reported at that grade. The same rule applies for solicited events ongoing at the end of the solicited follow-up period considering the maximum intensity reported.

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered general events since the administration site flag is not included in the expedited adverse event eCRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarised, each event recorded as having occurred during a specific period will be counted as the number of occurrences the event is consecutively reported (at Grade 1 or higher). When the occurrences of solicited adverse events at a specific grade are summarised, each event recorded as having occurred at that grade during a specific period will be counted as the number of occurrences the event is consecutively reported at that grade.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with 1 more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with 1 decimal will be displayed with 2 decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, BMI, pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values below 10kg where 1 decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with 1 decimal.

10.1.4.4. Serological summary statistics

The number of decimals used when displaying GMCs and their confidence limits is shown in the following table:

GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the 1 with the higher number of decimals). For example, if GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Mietinnen and Nurminen [Miettinen, 1985].

10.1.5.3. Adjusted GMC ratios

When between-group GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

10.2. TFL ToC

The list of tables, figures and listings (TFL ToC) planned for this study can be found in eTMF folder section 11.1.1.

10.3. Randomization method and minimization algorithm

The minimization algorithm used at the GSK internet randomization system (i.e. SBIR) for study NTHI MCAT-009 is based on the following reference: "*White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978; 37: 849-857*" [White, 1978] and it is described below:

Notations

- K=3 input values [Centre, Smoking status and Age category] to be used for minimization, each with a weight w_k=1 (k=1,.., K) & l_k variants.
- I=4 treatment groups [NTHi-Mcat, Sh_NTHi-Mcat_6, Sh_NTHi-Mcat_3, Sh_NTHi-Mcat_1] with randomization ratio $a_1,\ldots,a_I$ [1:1:1:1]

Algorithm

For a new subject with input value variants $s_1 \ldots s_K$

Step 1: Minimization computation

Step 1.1: Initialize Problem flag to 0

For each input value variant s_k, compute the number of subjects already enrolled in each treatment group.

Let b_{ik} the number for treatment i & input value variant s_k: b_{ik} is the total number of subjects already randomized in treatment i and with variant s_k.

Step 1.2: For each treatment i: compute $A_i = 1/a_i * sum_k(w_k*b_{ik})$

Step 2: determine whether the algorithm is random or deterministic:

Generate R, a random number within [0-1], uniform distribution

Step 3: check determinism

If R < 0.9, go to step 4 (determinism) else go to step 5 (random)

Step 4: determinism

4.1: Identify all treatments with the lowest value A_i

4.2: Select randomly one of the treatments identified in step 4.1, let it be T.

Go to step 6, if no more treatment then randomization failed

Step 5: randomization

Select randomly one of the treatments, let it be T.

Go to step 6, if no more treatment then randomization failed.

Step 6: treatment allocation

Assign one of the treatment nr. related to treatment T in the subject's center.

If no treatment nr. related to treatment T is available in the subject's center, then go & repeat step 4 (determinism) or 5 (random) while dropping treatment T (set problem flag=1).

11. REFERENCES

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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Immunogenicity and safety study of GSK's investigational vaccine (GSK3277511A) when administered in healthy smokers and ex-smokers following receipt of *Shingrix* vaccine.
eTrack study number and Abbreviated Title	209538 (NTHI MCAT-009)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 01 April 2019
Co-ordinating author:	PPD (Statistician)
Reviewed by:	• PPD (Clinical & Epidemiology Project Lead) • PPD (Clinical Research & Development Lead) • PPD (Lead Statistician) • PPD (Lead Statistical Analyst) • PPD (Statistical Analyst) • PPD (Scientific writer) • PPD (Stat Peer Reviewer) • PPD (Regulatory Affairs) • PPD (SERM scientist) • PPD (Public disclosure representative)
Approved by:	• PPD (Clinical & Epidemiology Project Lead) • PPD (Clinical Research & Development Lead) • PPD (Lead Statistician) • PPD (Statistician) • PPD (Scientific writer) • PPD (Lead Statistical Analyst)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 12th November 2018)

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LIST OF ABBREVIATIONS

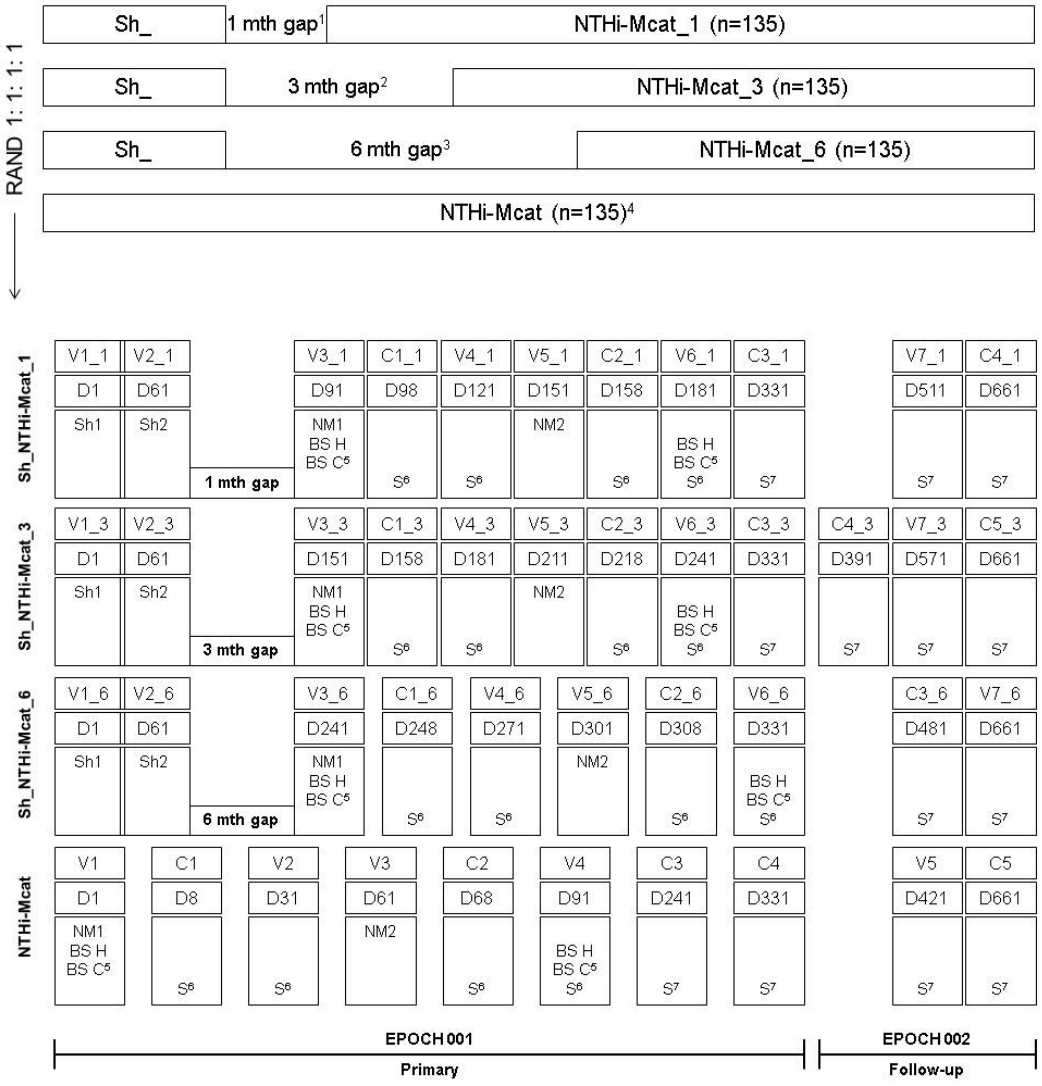
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CMI	Cell-Mediated Immune
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EU/mL	ELISA unit per milliliter
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
eTMF	Electronic Trial Master File
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMR	Geometric mean ratio
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NI	Non-Inferiority
PD	Protocol Deviation
PPS	Per-Protocol Set
RCD	Reverse cumulative distribution
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
TFL	Tables Figures and Listings
ToC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
01 APR 2019	Final version	Protocol Administrative Change 1: 14 DEC 2018

2. STUDY 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. Patients 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 of the study protocol 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

- **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).
- **End of Study (EoS):** Last subject last visit (Day 661).
- **Study groups:** Approximately 540 eligible subjects who will be randomly assigned to 4 study groups in a (1: 1: 1: 1) ratio (Table 1). Please refer to Section 10.1 of the protocol for details related to the determination of sample size.

Table 1 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*

- **Treatment allocation:** Subjects will be allocated to a study group using an automated, electronic System Built for Internet Randomization (SBIR). The randomization algorithm will use a minimization 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.
- **Blinding:** open-label.
- **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:** 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 7-day follow-up period after each NTHi-Mcat vaccination; 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, potential immune-mediated diseases (pIMDs), throughout the whole study period.

3. 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]
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.

Objectives	Endpoints
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]
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 and as such the Visit/contact label varies. Please refer to the study design diagram (Figure 1).

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

[3] Refer to Section 5.3.1 of the study protocol for details regarding the CMI sub-cohort.

4. ANALYSIS SETS

4.1. Definition

Analysis Set	Description
Enrolled	All subjects who signed informed consent
Exposed (ES)	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 (FAS)	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 (PPS)	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[1] (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[1] (exposed set) who have solicited safety data

[1] Study treatment refers to the NTHi-Mcat vaccine. Please refer to Section 4.1.1 for additional details.

4.1.1. Additional considerations

For the Unsolicited and Solicited safety sets, 1 dose of the study treatment refers to the administration of at least 1 dose of the NTHi-Mcat vaccine, in line with the study analysis of solicited and unsolicited AEs. In addition, subjects exposed to *Shingrix* only (if any) will be included in an extra group named "Shingrix only" for the safety analyses based on the Exposed Set (ES). Refer to Section 9.1.2 for more details about the algorithm to attribute subjects to groups for the purpose of safety analyses.

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) will be used for identifying subjects eliminated from the ES.

Subjects assigned to code 1030.b (not administering any NTHi-Mcat vaccine), but not to code 1030 will be identified as subjects belonging to the "Shingrix only" group.

4.2.2. Elimination from Full analysis set (FAS)

4.2.2.1. Excluded subjects

A subject will be excluded from the FAS analysis under the following conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
800	Fraudulent data	All	HUM, CMI
900	Invalid informed consent	All	HUM, CMI
1030	Study vaccine not administered at all	All	HUM, CMI
2100.a	Humoral immune response results not available post-vaccination	V6_1, V6_3, V6_6, V4	HUM
2100.b	CMI response results not available post-vaccination	V6_1, V6_3, V6_6, V4	CMI
2130	Subject bled but blood sample not planned per study protocol	Elimination is specific to the samples not planned per protocol (subject is retained)	HUM, CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.

4.2.3. Elimination from Modified full analysis set (mFAS)

4.2.3.1. Excluded subjects

A subject will be excluded from the mFAS analysis if excluded from the FAS and under the following additional conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
1070.a	Incomplete treatment course	All	HUM, CMI
1070	Other deviations related to wrong treatment administered (including randomization failure)	All	HUM, CMI
2080	Subjects did not comply with Sh_NTHi-Mcat vaccination schedule	V3_1, V3_3, V3_6	HUM, CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.

4.2.4. Elimination from Per-protocol analysis set (PPS)

4.2.4.1. Excluded subjects

A subject will be excluded from the PPS analysis if excluded from the mFAS and under the following additional conditions:

Code	Condition under which the code is used	Visit (V) (timepoints) where the code is applicable	Applicable for endpoint [HUM=humoral response, CMI=CMI response]
1040	Administration of concomitant vaccine(s) forbidden in the protocol	All	HUM, CMI
1070	Vaccination not according to protocol	All	HUM, CMI
1080	Vaccine temperature deviation	All	HUM, CMI
1090	Expired vaccine administered	All	HUM, CMI
2010	Protocol violation (inclusion/exclusion criteria)	All	HUM, CMI
2040	Administration of any medication forbidden by the protocol	All	HUM, CMI
2050	Medical condition forbidden by the protocol	All	HUM, CMI
2080	Subjects did not comply with vaccination schedule	All	HUM, CMI
2090.a	Subjects did not comply with blood sample schedule (sample for humoral immune response)	All	HUM
2090.b	Subjects did not comply with blood sample schedule (sample for CMI response)	All	CMI
2100.a	Humoral immune response results not available	All	HUM
2100.b	CMI response results not available	All	CMI
2120.a	Obvious incoherence or abnormality or error in data (data on humoral immune response)	All	HUM
2120.b	Obvious incoherence or abnormality or error in data (data on CMI response)	All	CMI

Note: CMI elimination codes are applicable only to subjects belonging to the CMI sub-cohort.

4.2.5. Elimination from unsolicited and solicited safety set

4.2.5.1. Excluded subjects

4.2.5.1.1. Unsolicited safety set

Code 1030.b (not administering any NTHi-Mcat vaccine), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used to identify subjects eliminated from the unsolicited safety set.

Code 1150 will be attributed to subjects if all the following conditions are met: subject did not complete the safety assessment following the 7-day follow-up period after NTHi-Mcat vaccinations (i.e. phone contacts), did not return the pDiary, did not return for the scheduled visit 30-days after the NTHi-Mcat vaccinations and did not report any unsolicited AE.

4.2.5.1.2. Solicited safety set

Code 1030.b (not administering any NTHi-Mcat vaccine), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used to identify subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

Note that standard data derivation rules and statistical methods are described in "business rules document" and will not be repeated below. The study specific data derivation rules and statistical methods will be described in Section 9.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

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 PPS and mFAS will be tabulated.

5.1.2. Additional considerations

Summaries of demographic/baseline characteristics will include: age, country, centre, gender, race, ethnicity, smoking status, pack-years and vital signs (including body mass index [BMI]).

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

None.

5.2.2. Additional considerations

The number and percentage of subjects who received study vaccine doses will be tabulated for each study group (based on the ES).

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

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

Endpoint	Statistical analysis methods
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.
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

Endpoint	Statistical analysis methods
	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).

5.3.2. Additional considerations

The supplementary analysis based on the mFAS will be performed if the percentage of mFAS subjects excluded from the PPS is more than 10%.

5.3.2.1. Analysis of humoral response

Hypothesis related to the primary objective

The global null hypothesis related to the primary objective of the study is that at least 1 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. Family-wise type I error is fixed at 2.5% (1-sided).

Geometric mean concentration and geometric mean concentration ratio

For each antigen and study group, at 1 month after Dose 2 of NTHi-Mcat vaccine, adjusted GMCs and GMCs ratios with corresponding 95% CIs will be obtained exponentiating (base 10) the least square means and the lower and upper limits of the 95% CIs derived from the ANCOVA model. The ANCOVA model will be implemented in SAS, similarly to the following code:

```
PROC GLM data=<dataset>;
BY antigen;
class group age smoking_status centre;
MODEL log(concentr)= group age smoking_status centre log(pre_concentr);
LSMEAN group / CL PDIFF ALPHA=0.05;
RUN;
```

Contrasts to be included: Sh_NTHi-Mcat_6 vs NTHi-Mcat, Sh_NTHi-Mcat_3 vs NTHi-Mcat, Sh_NTHi-Mcat_1 vs NTHi-Mcat.

In addition, unadjusted GMCs and GMRs will be presented for each timepoint (pre-Dose 1 and post-Dose 2 of NTHi-Mcat vaccine) with a descriptive purpose.

Permutation test (sensitivity analysis on primary objectives)

Based on the covariate-adaptive treatment assignment algorithm (see Section 10.3), the following permutation test will be performed as a sensitivity analysis on the primary objectives [Wiens, 2006, Hasegawa, 2009 and Ernst, 2004] in the PPS.

For each antigen, let $\mathbf{X}=(X_1, \ldots, X_N)$ the logarithmically-transformed antibody concentrations for the NTHi-Mcat group and $\mathbf{Y_{1/3/6}}=(Y_1, \ldots, Y_N)$ the logarithmically-transformed antibody concentrations for one of the Sh_NTHi-Mcat groups at 1 month after Dose 2 of NTHi-Mcat vaccine, a non-inferiority permutation test can be obtained from a superiority permutation test on $\dot{\mathbf{X}}=(X_1, \ldots, X_N)$ against $\dot{\mathbf{Y}}_{\mathbf{1/3/6}}=(Y_1 + \delta, \ldots, Y_N + \delta)$ with $\delta = 0.176 = -\log_{10}(0.667)$.

The original treatment assignment algorithm will be used to re-randomize subjects belonging to the NTHi-Mcat group and, individually, each of the Sh_NTHi-Mcat groups (see step 2a) while keeping antibody concentrations, covariates and entry order as observed. This is in line with the experimental design comparing individually 3 treatment groups with a unique control group. The procedure will be as follows:

1. Fit the ANCOVA model to obtain the test statistics $T^*_{1/3/6}$ for the superiority of $\dot{\mathbf{X}}$ against $\dot{\mathbf{Y}}_{\mathbf{1/3/6}}$.
2. For each of the Sh_NTHi-Mcat_**k** groups [k=1, 3, 6], estimate the distribution of the corresponding test statistics with R=10000 repetitions of the following 2 steps:
   a. Re-randomize treatment assignment of groups $\dot{\mathbf{X}}$ and $\dot{\mathbf{Y}}_{\mathbf{k}}$ alone (original algorithm), while keeping the remaining 2 groups fixed.
   b. Re-fit the full ANCOVA model to re-obtain the test statistics T_k
3. Derive the permutation p-values associated to the observed test statistics (from step 1) based on the empirical distributions in Step 2

$\mathbf{p}_{1/3/6} = M+1/R+1$

Where M is the number of repetitions such that $T_{1/3/6} \geq T^*_{1/3/6}$.

Seropositivity rate and fold increase

For each antigen, timepoint and study group, the seropositivity rate (defined as the proportion of subjects with an antibody concentration greater or equal to the assay cut-off) with exact 95% CIs will be computed using the method referenced in section 10.1.5.1. Assay cut-offs are reported in section 9.1.1. In addition, percentages of subjects with a 2/4/8-fold increase will be presented with associated 95% CI.

Reverse cumulative distribution curves

Reverse cumulative distribution (RCD) curves for antibody concentrations will be plotted: the x-axis represents the antibody concentrations value (log-10 scale), while the

y-axis the percentage of subjects having a log-transformed antibody value greater or equal to the corresponding x-value.

5.3.2.2. Analysis of CMI response

The frequency of **antigen-specific** CD4+ or CD8+ T-cells for each individual subject is calculated as the difference between the frequency of CD4+ or CD8+ T-cells producing at least 2 activation markers among CD40 Ligand (CD40L), IL-2, TNF- α, IFN- γ, IL-13 and IL-17, upon *in vitro* stimulation with the antigen (induction condition) minus the frequency of CD4+ or CD8+ T-cells producing at least 2 activation markers upon in vitro stimulation in medium only (background condition). For descriptive statistics purposes, differences less or equal to zero (0) are imputed to 1.

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

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.

5.4.2. Additional considerations

5.4.2.1. Analysis of solicited AEs

The analysis of solicited AEs will be performed on the Solicited safety set.

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 (i.e. fever) 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

Fever, defined as a body temperature of ≥37.5°C irrespective of route of measurement, will be integrated to the summaries as a general AE.

In addition, body temperature will be broken down by 0.5°C increments:

- <36.0
- 36.0 – 36.4
- 36.5 – 36.9
- 37.0 – 37.4
- 37.5 – 37.9
- 38.0 – 38.4
- 38.5 – 38.9
- 39.0 – 39.4
- 39.5 – 39.9
- ≥40.0

Compliance of subjects in completing solicited AEs information will be reported as the percentage of subjects completing at least 80% of the diary entries related to local and general solicited AEs.

5.4.2.2. Analysis of unsolicited AEs

The analysis of unsolicited AEs will be performed on the Unsolicited safety set.

Analysis of unsolicited AEs will be also stratified on AEs with a causal relationship to NTHi-Mcat vaccination.

5.4.2.3. Combined analysis of solicited and unsolicited AEs

The combined analysis of solicited and unsolicited AEs will be performed on the Unsolicited safety set.

Solicited AEs will be coded by MedDRA as per the following codes:

Solicited symptom	Preferred Term code	Corresponding Preferred Term decode
Pain	10022086	Injection site pain
Redness	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Myalgia	10028411	Myalgia
Chills	10008531	Chills
Fever	10037660	Pyrexia

Combined analysis of solicited and unsolicited AEs will be also stratified on AEs with a causal relationship to NTHi-Mcat vaccination (all solicited AEs are considered causally related).

5.4.2.4. Analysis of SAEs and pIMDs

The analysis of SAEs and pIMDs will be performed on the Exposed Set (ES).

Analysis of SAEs will include:

- All SAEs from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
- Fatal SAEs from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
- Related SAEs:
  - To any study vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.
  - To the NTHi-Mcat vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661, from the day of the first NTHi-Mcat vaccination up to 1 month following the second dose, from the day of the first NTHi-Mcat vaccination up to 6 months following the second dose and from the day of the first NTHi-Mcat vaccination up to 12 months following the second dose (all groups except “Shingrix only”).
  - To *Shingrix* vaccine, from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661 (all groups except NTHi-Mcat).

Analysis of pIMDs will include all occurrences from Day 1 to Day 331, from Day 331 to Day 661 and from Day 1 to Day 661.

5.4.2.5. Other safety analyses

Medications will be coded using GSKDRUG dictionary.

All collected concomitant medications and vaccinations will be listed. In case of pregnancies during the study, follow-up data and pregnancy outcomes will be described in detail.

6. ANALYSIS INTERPRETATION

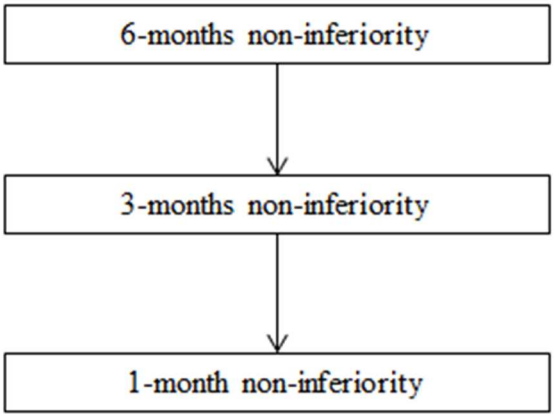
Except for analysis on primary objectives, with predefined success criteria and an appropriate type I error control, comparative analyses are descriptive with the aim to characterize the difference between groups.

With respect to confirmatory analyses on primary objectives the interpretation will be done in a hierarchical manner.

Each objective can only be reached if all the associated criteria are met and all previous objectives have been reached (see Figure 2): starting from the 6-months lag, the 3-months NI can be achieved only if the 6-months NI is demonstrated, while the 1-month NI can be achieved only if the 6-months and 3-months NI are both demonstrated.

This sequential procedure enables to control the overall type I error below 2.5% (one-sided) [Dmitrienko, 2009].

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



7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The integrated clinical study report (CSR) 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 CSR containing all data from Epoch 001 and Epoch 002 will be written and made available to the investigators.

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final Analysis Epoch 001	Web disclosure (CTRS), Study report (SR)
Analysis of Follow-up Epoch	Web disclosure (CTRS), Study report (SR)

7.2. Statistical considerations for 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.

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in Section 10.1

9.1. Data derivation

9.1.1. Assay cut-offs for serology results

Component	Method	Unit[1]	Assay cut-off[1]
anti-PD antibody	ELISA	EU/mL	153
anti-PE antibody	ELISA	EU/mL	25
anti-PilA antibody	ELISA	EU/mL	16
anti-UspA2 IgG antibody	ELISA	EU/mL	38

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.

9.1.2. Attributing subjects to time-lag groups

For the purpose of safety analyses, the following rule will be used to attribute exposed subjects to a specific group.

- If a subject receives no *Shingrix* vaccination → NTHi-Mcat group
- If a subject receives at least 1 *Shingrix* vaccination, but no NTHi-Mcat vaccination → "Shingrix only" group
- If a subject receives at least 1 *Shingrix* vaccination and at least 1 NTHi-Mcat vaccination, the difference, in days, between the latest Shingrix vaccination and the earliest NTHi-Mcat vaccination will be computed and converted in months (diff):
  - diff ≤ 2 → Sh_NTHi-Mcat_1 group
  - $2 <$ diff ≤ 4.5 → Sh_NTHi-Mcat_3 group
  - diff > 4.5 → Sh_NTHi-Mcat_6 group

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in Section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the eCRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.

- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited symptoms

10.1.2.3.1. Studies with paper diaries

Denominators for the summary of local (or general) solicited symptoms will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of local (or general) symptoms.

When a specific symptom is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the symptom in question), all daily measurements will be imputed as Grade 0.

When a specific symptom is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the symptom in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

When the occurrence of a specific symptom is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of symptoms (local or general) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

The following table shows how subjects contribute to each category for a specific solicited symptom over the Day X to Day Y post-vaccination period:

Solicited symptom category	Subjects included in the calculation of the numerator
Any	All subjects with at least one occurrence of the symptom at Grade 1, Grade 2, or Grade 3 between Day X and Day Y or with the symptom marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All subjects with at least one occurrence of the symptom at Grade 1, Grade 2, or Grade 3 between Day X and Day Y
At least grade 2	All subjects with at least one occurrence of the symptom at Grade 2 or Grade 3 between Day X and Day Y
At least grade 3	All subjects with at least one occurrence of the symptom at Grade 3 between Day X and Day Y

10.1.2.4. Unsolicited adverse events

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.2. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (weight in kilograms) / (height in meters)^2

10.1.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

10.1.3.4. Geometric mean concentrations (GMCs)

GMC calculations are performed by taking the inverse logarithm of the mean of the log-10 concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.5. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

10.1.3.6. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus 1 day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the symptom reported at Grade 1 or higher.

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered general events since the administration site flag is not included in the expedited adverse event eCRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarised, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study vaccines, an injection site reaction recorded for a subject following multiple vaccines will be counted as only one occurrence.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
    - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with 1 more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with 1 decimal will be displayed with 2 decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, BMI, pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values below 10kg where 1 decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with 1 decimal.

10.1.4.4. Serological summary statistics

The number of decimals used when displaying GMCs and their confidence limits is shown in the following table:

GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the 1 with the higher number of decimals). For example, if GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Mietinnen and Nurminen [Miettinen, 1985].

10.1.5.3. Adjusted GMC ratios

When between-group GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

10.2. TFL ToC

The TFL ToC can be found in eTMF folder section 11.1.1.

10.3. Randomization method and minimization algorithm

The minimization algorithm used at the GSK internet randomization system (i.e. SBIR) for study NTHI MCAT-009 is based on the following reference: "*White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978; 37: 849-857*" [White, 1978] and it is described below:

Notations

- K=3 input values [Centre, Smoking status and Age category] to be used for minimization, each with a weight w_k=1 (k=1,.., K) & l_k variants.
- I=4 treatment groups [NTHi-Mcat, Sh_NTHi-Mcat_6, Sh_NTHi-Mcat_3, Sh_NTHi-Mcat_1] with randomization ratio $a_1,\ldots,a_I$ [1:1:1:1]

Algorithm

For a new subject with input value variants $s_1 \ldots s_K$

Step 1: Minimization computation

Step 1.1: Initialize Problem flag to 0

For each input value variant s_k, compute the number of subjects already enrolled in each treatment group.

Let b_{ik} the number for treatment i & input value variant s_k: b_{ik} is the total number of subjects already randomized (excluding subjects cancelled/withdrawn prior dose 1) in treatment i and with variant s_k.

Step 1.2: For each treatment i: compute $A_i = 1/a_i * sum_k(w_k*b_{ik})$

Step 2: determine whether the algorithm is random or deterministic:

Generate R, a random number within [0-1], uniform distribution

Step 3: check determinism

If $R < 0.9$, go to step 4 (determinism) else go to step 5 (random)

Step 4: determinism

4.1: Identify all treatments with the lowest value A_i

4.2: Select randomly one of the treatments identified in step 4.1, let it be T.

Go to step 6, if no more treatment then randomization failed

Step 5: randomization

Select randomly one of the treatments, let it be T.

Go to step 6, if no more treatment then randomization failed.

Step 6: treatment allocation

Assign one of the treatment nr. related to treatment T in the subject's center.

If no treatment nr. related to treatment T is available in the subject's center, then go & repeat step 4 (determinism) or 5 (random) while dropping treatment T (set problem flag=1).

11. REFERENCES

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