	STATISTICAL ANALYSIS PLAN
Detailed Title:	A Phase IIIB, Randomized, Observer-blind, Multicenter Study to Assess the Safety and Immunogenicity of GSK Meningococcal Group B Vaccine when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine to Healthy Subjects 16-18 Years of Age.
eTrack study number and Abbreviated Title	205419 (MENB REC 2ND GEN-045 (V72_79))
Scope:	All analyses for the primary and secondary objectives of the study. CCI [redacted].
Date of Statistical Analysis Plan	Amendment 3 Final: 03 Jun 2024

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

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
DOB	Date of Birth
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMR	Geometric mean ratio
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
hSBA	Human Serum Bactericidal Assay
IU/mL	International units per milliliter
LLOQ	Lower Limit of Quantification
LOD	Limit of Detection
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content

1. DOCUMENT HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	17 September 2019	Amendment 1: 14 August 2019	Not Applicable	Original version
SAP amendment 1	13 January 2022	Amendment 5: 15 April 2021	CCI [redacted] • Footnote updated in objective table • Unsolicited and solicited safety set sections added • Title section 4.7.3.1.1 and 4.7.3.1.2 updated • Section 5.1.2 addition of analysis regarding COVID-19 • Section 6.1 change in the testing strategy	CCI [redacted] • Clarification that reporting of changes to the NHBA strain during the study will be documented in the clinical study report. • Safety analysis will finally use those sets and not the exposed set • To fit the addition of the two unsolicited and solicited sets • addition of analysis regarding COVID-19 to fit guidelines

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				• Section 6.1 change in the strains testing strategy to have all strains tested
SAP Amendment 2	13 December 2022	Amendment 7: 11 October 2022	• Section 2 updated primary safety endpoints to split assessment according to SFU period • Section 3 change in study design graphical representation and definitions • Table 3 extension of allowed visit window • Section 5.5.1.2 change in Unsolicited AEs analysis	• In Protocol Amendment 7 the safety follow-up period has been shortened to 6 months in subjects who have not reached the 6-month safety follow-up after the last dose, at the time the amendment takes effect • SFU changed • Aims to mitigate the impact of COVID pandemic • Endpoint update
SAP Amendment 3	03 Jun 2024	Amendment 7: 11 October 2022	• Section 4 updated to remove unsolicited and solicited safety sets • Table 5 updated	• Safety analyses will be conducted on the exposed set • Alignment with current assay LOD, LLOQ and ULOQ values

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			• Section 5.5.1.1 updated to include analyses of Solicited AEs duration and onset day • Section 5.5.1.1 updated to track handling strategy for duplicate AEs • Section 5.5.1.2 added eDiary compliance analysis • Section 5.5.1.3 change to add definition and analysis of immediate unsolicited AEs • Section 8 added change in assay methodology • Section 10.1.3.11 updated Solicited AEs duration definition	• Safety analyses update • Safety analysis clarification • Alignment with eCOA compliance expectations • Alignment with current expectations • Track change in assay methodology and impact on analyses • Alignment with current expectations

2. OBJECTIVES/ENDPOINTS

Objectives and endpoints are detailed in the table below:

Objectives	Endpoints
	Primary

To assess the safety and tolerability of rMenB+OMV NZ and MenACWY, when administered concomitantly or alone, in healthy subjects 16-18 years of age.	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups.
	• The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 30 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups.
	• The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, throughout the study period (Day 1/Month 0 to Month 9).
	• The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI throughout the study period (Day 1/Month 0 to Month 9).
	• Among subjects who are followed for 12 months after their last dose:
	  ○ The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, between SFU 5/Month 9 and SFU 7/Month 15
	  ○ The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI between SFU 5/Month 9 and SFU 7/Month 15.

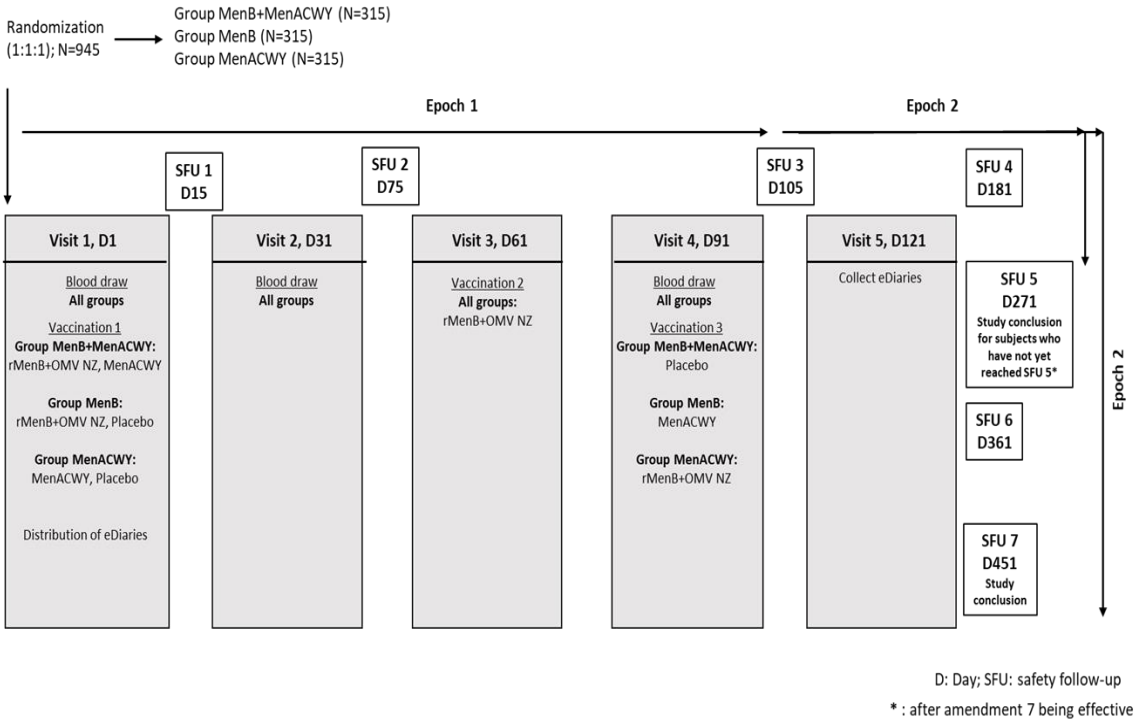
To demonstrate the non-inferiority of the antibody response to rMenB+OMV NZ given concomitantly with MenACWY to healthy subjects 16-18 years of age compared to rMenB+OMV NZ administered alone, as measured by serum bactericidal assay using human complement (hSBA) Geometric Mean Titers (GMTs) against *N. meningitidis* serogroup B indicator strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA), at one month after the second vaccination with rMenB+OMV NZ. *Criterion: Non-inferiority will be demonstrated if for each of the four serogroup B test strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus rMenB+OMV NZ alone) is >0.5.*	Co-primary endpoints for Group MenB+MenACWY and Group MenB are the hSBA GMTs for rMenB+OMV NZ against each of the four serogroup B test strains (M14459, 96217, NZ98/254 and M07-0241084) at one month after the second vaccination with rMenB+OMV NZ (Visit 4, Month 3).

Objectives	Endpoints
To demonstrate the non-inferiority of the antibody response to MenACWY given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone, as measured by hSBA GMTs against each of the *N. meningitidis* serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY. *Criterion: Non-inferiority will be demonstrated if for each of the four serogroups A, C, W and Y, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus MenACWY alone) is >0.5.*	Co-primary endpoints for Group MenB+MenACWY and Group MenACWY are the hSBA GMTs against each of the four serogroups A, C, W and Y with MenACWY at one month after the study vaccination of MenACWY (Visit 2, Month 1).
Secondary	
To assess the non-inferiority of the responses to MenACWY when given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone as measured by Enzyme-Linked Immunosorbent Assay (ELISA) Geometric Mean Concentration (GMCs) against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY. *Criterion: Non-inferiority will be demonstrated if for each of the four A, C, W and Y strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of ELISA GMCs (MenACWY with rMenB+OMV NZ versus MenACWY alone) is >0.5.*	**Immune response to MenACWY** The immune response to MenACWY when administered with/without rMenB+OMV NZ one month after the first vaccination (Visit 2, Month 1, Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as ELISA GMCs.
To assess the immune response to rMenB+OMV NZ in healthy subjects 16-18 years of age against *N. meningitidis* serogroup B test strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA), at one month after the first and the second vaccination with rMenB+OMV NZ.	**Immune response to rMenB+OMV NZ** The immune response to rMenB+OMV NZ when administered with/without MenACWY will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B test strains M14459, 96217, NZ98/254 and M07-0241084 in both MenB+MenACWY and MenB Groups as following: • GMTs at one month after first (Visit 2, Month 1) and second (Visit 4, Month 3) vaccination with rMenB+OMV NZ and Geometric Mean Ratio (GMRs) at one month after the first and the second rMenB+OMV NZ vaccination compared to the baseline at Visit 1, Day 1/Month 0. • The percentage of subjects with hSBA titers ≥ Lower Limit of Quantitation (LLOQ) for each and all serogroup B test strains, one month after the first (Visit 2, Month 1) and second (Visit 4, Month 3) vaccination. • The percentage of subjects with fourfold increase in hSBA titers relative to baseline (Visit 1, Day 1/Month 0) defined as: – For a pre-vaccination titer < limit of detection (LOD), a post-vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater,

Objectives	Endpoints
	– For a pre-vaccination titer ≥LOD but <LLOQ, a post vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the LLOQ, – For a pre-vaccination titer ≥ LLOQ, a post vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the pre-vaccination titer (for Groups MenB+MenACWY and MenB). • The ratio of GMTs (rMenB+OMV NZ when administered with MenACWY [Group MenB+MenACWY] versus rMenB+OMV NZ when administered alone [Group MenB]), one month after the first vaccination (Visit 2, Month 1).
To assess the immune response to MenACWY in healthy subjects 16-18 years of age against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY.	**Immune response to MenACWY** The immune response to MenACWY when administered with/without rMenB+OMV NZ at baseline (i.e. pre-vaccination, Visit 1, Day 1/Month 0) and at one month after the first vaccination (Visit 2, Month 1; Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as: • The percentage of subjects with hSBA titers ≥LLOQ, for each serogroup. • GMRs at one month after first vaccination compared to baseline • The percentage of subjects with fourfold increase in hSBA titers relative to baseline (Visit 1, Day 1/Month 0) is defined as: – For a pre-vaccination titer < LOD, a post-vaccination titer (Visit 2, Month 1) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater, – For a pre-vaccination titer ≥LOD but <LLOQ, a post vaccination titer (Visit 2, Month 1) of at least fourfold the LLOQ, – For a pre-vaccination titer ≥ LLOQ, a post vaccination titer (Visit 2, Month 1) of at least fourfold the pre-vaccination titer (for Groups MenB+MenACWY and MenACWY).
CCI [redacted]	[redacted]

*The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

3. STUDY DESIGN



Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, are essential and required for study conduct.

Approximately 945 subjects will be screened to achieve 750 evaluable subjects for an estimated total of 250 evaluable subjects per treatment group. Withdrawals will not be replaced.

- Type of study: self-contained
- Experimental design: Phase IIIB, observer-blind, randomised, controlled, multi-centric, study with 3 parallel groups.
- Duration of the study:
  - Epoch 001: Primary starting at Visit 1 (Day 1) and ending at Visit 4 (Day 91)
  - Epoch 002: Safety follow-up period starting at Visit 4 (Day 91) and ending at Study termination-call (Day 451 [Month 15] or Day 271 [Month 9] for subjects who have not reached Day 271 at the time Protocol Amendment 7 takes effect)
- Primary Completion Date (PCD): Study termination-call (Day 451 [Month 15] or Day 271 [Month 9] for subjects who have not reached Day 271 at the time Protocol Amendment 7 takes effect)
- End of Study (EoS): Last subject last visit (LSLV) [last concluding contact on Day 451 (Month 15) or Day 271 (Month 9) for subjects who have not reached Day 271 at the time Protocol Amendment 7 takes effect] or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and

secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

- Study groups:
  - Group MenB+MenACWY: rMenB+OMV NZ given concomitantly with MenACWY at study Day 1; rMenB+OMV NZ at study Day 61; Placebo at study Day 91.
  - Group MenB: rMenB+OMV NZ given concomitantly with Placebo at study Day 1 and rMenB+OMV NZ at study Day 61; MenACWY at study Day 91.
  - Group MenACWY: MenACWY given concomitantly with Placebo at study Day 1; rMenB+OMV NZ at study Day 61 and at study Day 91.

Table 1 Study groups, treatment and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name	Epochs (Blinding)	
					Epoch 001 (observer-blind)	Epoch 002 (observer-blind)
MenB+MenACWY	315	16 years – 18 years	*Bexsero*	rMenB+OMV NZ	x	x
			Menveo	MenACWY (MenA lyo+MenCWY liquid		
			Placebo	*NaCl*		
MenB	315	16 years – 18 years	*Bexsero*	rMenB+OMV NZ	x	x
			Menveo	MenACWY (MenA lyo+MenCWY liquid		
			Placebo	*NaCl*		
MenACWY	315	16 years – 18 years	*Bexsero*	rMenB+OMV NZ	x	x
			Menveo	MenACWY (MenA lyo+MenCWY liquid		
			Placebo	*NaCl*		

Table 2 Overview of study design: Vaccination and Blood Draw Schedule

Visits Study Day	Visit 1 Day 1	Visit 2 Day 31	Visit 3 Day 61	Visit 4 Day 91
Group MenB+MenACWY N=315	Blood Draw rMenB+OMV NZ MenACWY	Blood Draw	rMenB+OMV NZ	Blood Draw Placebo
Group MenB N=315	Blood Draw rMenB+OMV NZ Placebo			Blood Draw MenACWY
Group MenACWY N=315	Blood Draw MenACWY Placebo			Blood Draw rMenB+OMV NZ

- Control: active control.
- Vaccination schedules: Day 1 (Visit 1), Day 61 (Visit 3) and Day 91 (Visit 4)
- Treatment allocation: Subjects to be randomised in a 1:1:1 ratio at Visit 1 (Day 1) to Groups MenB+MenACWY, MenB and MenACWY.
- Blinding: observer-blind.
- Sampling schedule:
  - Blood sampling: For all the 3 groups (i.e., Group MenB+MenACWY, Group MenB, and Group MenACWY), approximately 20 mL sample of blood will be drawn at Visit 1 (Day 1) before the first vaccination, at Visit 2 (Day 31) and at Visit 4 before vaccination (Day 91).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects at Visit 1, Visit 3 and Visit 4 prior to the vaccinations.

Data collection: Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).

Whenever possible, the investigator should arrange study visits within the intervals described in the below table.

Table 3 Visit interval

Interval	Length of interval	Allowed interval
Visit 1 → Visit 2	30 days	23 - 58 days
Visit 1 → Visit 3	60 days	53 - 88 days
Visit 3 → Visit 4	30 days	23 - 58 days
Visit 4 → Visit 5	30 days	23 - 58 days

4. ANALYSIS SETS

4.1. Enrolled Set

All subjects who signed inform consent.

4.2. Exposed Set

All subjects that received at least one dose of the study treatment. The allocation to a group is done in function of the administered treatment.

4.3. Full Analysis Set

All subjects who received at least one dose of the study treatment and have post-vaccination immunogenicity data.

4.4. Per Protocol Set

All subjects who received at least one dose of the study treatment to which they are randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion. PDs leading to a Per Protocol Set exclusion are detailed in Section 4.5.2.

4.5. Criteria for eliminating data from Analysis Sets

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

4.5.1. Elimination from Exposed Set (ES)

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

4.5.2. Elimination from Per-protocol analysis Set (PPS) and Full Analysis Set (FAS)

4.5.2.1. Excluded subjects

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

Table 4 Exclusion codes

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	Visits 1, 3 and 4	All
1040	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 1, 2 (before BS at M1)	PPS M1 and M3
1040	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 2 (after BS at M1), 3, 4 (before BS at M3)	PPS M3
1050	Randomisation failure	Visit 1	PPS M1 and M3
1060	Randomisation code was broken	All	PPS M1 and M3
1070	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 1	PPS M1

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
1070	Subjects got vaccinated with the correct vaccine but containing a lower volume	Visit 3	PPS M3
1070	Vaccination not according to protocol	Visit 1	PPS M1
1070	Vaccination not according to protocol	Visit 3	PPS M3
1080	Vaccine temperature deviation	Visit 1	PPS M1
1080	Vaccine temperature deviation	Visit 3	PPS M3
1090	Expired vaccine administered	Visit 1	PPS M1
1090	Expired vaccine administered	Visit 3	PPS M3
2010	Protocol violation (inclusion/exclusion criteria)	All	PPS M1 and M3
2040	Administration of any medication forbidden by the protocol	Visit 1, 2 (before BS at M1)	PPS M1 and M3
2040	Administration of any medication forbidden by the protocol	Visit 2 (after BS at M1), 3, 4 (before BS at M3)	PPS M3
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication (medical condition forbidden)	All	PPS M1 and M3
2060	Concomitant infection related to the vaccine which may influence immune response (only meningococcal infection)	All	PPS M1 and M3
2080	Subjects did not comply with vaccination schedule	Visit 1	PPS M1
2080	Subjects did not comply with vaccination schedule	Visit 3	PPS M3
2090	Subjects did not comply with blood sample schedule	Visit 2	PPS M1
2090	Subjects did not comply with blood sample schedule	Visit 4	PPS M3
2100	Serological results not available post-vaccination for any of the four *N. meningitidis* serogroup B indicator strains	Visit 2	FAS and PPS M1 (secondary objective)
2100	Serological results not available post-vaccination for any of the four *N. meningitidis* serogroup B indicator strains	Visit 4	FAS and PPS M3 (primary objective)

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2100	Serological results not available post-vaccination for any of the N. meningitidis serogroups A, C, W and Y (hSBA)	Visit 2	FAS and PPS M1 (primary objective)
2100	Serological results not available post-vaccination for any of the N. meningitidis serogroups A, C, W and Y (ELISA)	Visit 2	FAS and PPS M1 (secondary objective)
2120	Obvious incoherence or abnormality or error in data for any of the four *N. meningitidis* serogroup B indicator strains	Visit 2	FAS and PPS M1 (secondary objective)
2120	Obvious incoherence or abnormality or error in data for any of the four *N. meningitidis* serogroup B indicator strains	Visit 4	FAS and PPS M3 (primary endpoint)
2120	Obvious incoherence or abnormality or error in data for any of the N. meningitidis serogroups A, C, W and Y (hSBA)	Visit 2	FAS and PPS M1 (primary endpoint)
2120	Obvious incoherence or abnormality or error in data for any of the N. meningitidis serogroups A, C, W and Y (ELISA)	Visit 2	FAS and PPS M1 (secondary objective)
2130	Subject bled despite it was not planned to be bled	All	PPS M1 and M3
2170	Pregnancy	Visit 1	PPS M1 and M3
2170	Pregnancy	Visit 3	PPS M3

M1 and M3: months of the study schedule at which the subject will be eliminated from a specific population, i.e., Day 31 and Day 91.

5. STATISTICAL ANALYSES

That standard data derivation rules and stat methods are described in Section 10.1 while the study specific data derivation rules and stat methods are described in Section 9.

5.1. Demography

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

Descriptive statistics (mean, standard deviation [SD], median, minimum and maximum) for age, height, weight and body mass index (BMI) at enrolment will be calculated overall and by Group.

Distributions of subjects by sex, race, ethnic origin, geographical locations (US sites, non-US sites) and according to the pre-vaccination hSBA titer (per strain, <LLOQ or ≥LLOQ) will be summarized overall and by Group.

5.1.2. Additional considerations

Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, see Section 4.1 for enrolled definition, unless otherwise specified by the protocol.

The number of subjects with suspected, probable or confirmed COVID-19 infection will be summarized by treatment arm and across diagnoses. This summary will be provided for the exposed set.

The number of enrolled participants who discontinued the study will be tabulated by group with the reason for discontinuation. The summary table will be produced by relationship to COVID-19.

A summary table of important protocol deviation by relationship (related/not related) to COVID-19 will be provided.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccinations will be summarized overall and by vaccine group. Data will be tabulated for the All Enrolled Set.

5.2.2. Additional considerations

NA

5.3. Efficacy/Effectiveness

5.3.1. Analysis of efficacy planned in the protocol

NA

5.3.2. Additional considerations

NA

5.4. Immunogenicity

5.4.1. Analysis of immunogenicity planned in the protocol

5.4.1.1. Primary endpoints

The primary analysis will be conducted using the PPS for the primary (non-inferiority) objective. If, in any study group, the percentage of enrolled or vaccinated subjects with serological results excluded from the per-protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set (FAS) will be performed to complement the per-protocol analysis. Supportive analyses using the FAS will also be performed for the primary immunogenicity endpoints.

Within group assessment

- For Group MenB+MenACWY and Group MenB: hSBA GMTs for rMenB+OMV NZ against each of the four serogroup B test strains (M14459, 96217, NZ98/254 and M07-0241084) at one month after the second vaccination for rMenB+OMV NZ (Visit 4) will be calculated.
- For Group MenB+MenACWY and Group MenACWY: hSBA GMTs against each of the four serogroups A, C, W and Y for MenACWY at one month after the study vaccination of MenACWY (Visit 2) will be calculated.

Between group assessment

- The ratio of GMTs between Group MenB+MenACWY versus Group MenB when administered without MenACWY [Group MenB]), at one month after the second vaccination will be calculated.
- The ratio of GMTs between Group MenB+MenACWY versus Group MenACWY when administered alone [Group MenACWY], at one month after the study vaccination of MenACWY will be calculated.

Primary immunogenicity endpoints may be repeated using another panel of strains, if requested.

5.4.1.2. Secondary endpoints

The non-inferiority secondary objective is to be conducted using the PPS.

Within group assessment

- ELISA GMCs against each of the four serogroups A, C, W and Y at one month after the (study) vaccination for groups MenB+MenACWY and MenACWY.

- The percentage of subjects (and 2-sided 95% Clopper-Pearson CIs) with hSBA titers ≥LLOQ for each and all serogroup B test strains after the first and second vaccination for Groups MenB+MenACWY and MenB; and for serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY.
- hSBA GMTs against each of the four serogroups B test strains at baseline and one month after first vaccination with rMenB+OMV NZ for Groups MenB+MenACWY and MenB.
- GMRs (compared to baseline) against each serogroup B test strains at one month after the first and second vaccination for Groups MenB+MenACWY and MenB and one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY.
- The percentage of subjects (and 2-sided 95% Clopper-Pearson CIs) with fourfold increase in hSBA titers relative to baseline for each serogroup B test strains at one month after the first and the second vaccination for Groups MenB+MenACWY and MenB; and for serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY.

Between group assessment

- For all four serogroups A, C, W and Y, noninferiority of the responses to MenACWY when given with rMenB+OMV NZ compared to MenACWY administered alone will be assessed in terms of ELISA GMC.
- The ratio of GMTs between Group MenB+MenACWY versus Group MenB when administered alone at one month after the first vaccination, will be calculated.
- Between group differences (Group MenB+MenACWY vs Group MenB and Group MenB+MenACWY vs Group MenACWY), at one month after the first and the second vaccination (as applicable) will be calculated, as well as their associated 95% CIs.

5.4.2. Additional considerations

For each and all *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217 and NZ98/254) and each of the serogroups A, C, W and Y, the percentage of subjects with hSBA titers ≥ lower limit of quantitation (LLOQ) and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934] for each study group at baseline and at one month after the 1st vaccination and at one month after the 2nd vaccination, for serogroup B test strains, and at one month after (study) vaccination of MenACWY, for serogroups A, C, W and Y.

The hSBA titers/ELISA concentrations at each blood draw visit for each study group will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217 and NZ98/254) and each of the serogroups A, C, W and Y, the GMTs/GMCs and GMRs (compared to baseline) will be calculated, with their associated two-sided 95% CIs, by

exponentiating the corresponding log-transformed means and within-subject mean difference, respectively and their 95% CIs.

The ratio of GMTs between the Group MenB+MenACWY versus Group MenB at one month after the first and the second vaccination, and the corresponding CI will be constructed by exponentiating the mean difference and the confidence limits in log10 (titer), using ANOVA with study centre included as an independent variable.

The ratio of GMTs/GMCs between the Group MenB+MenACWY versus Group MenACWY at one month after the (study) vaccination of MenACWY, and the corresponding CI will be constructed the same way, by exponentiating the mean difference and the confidence limits in log10 (titer/concentration), using ANOVA with study centre included as an independent variable.

Summary tables will show adjusted GMTs/GMCs and adjusted ratios of GMTs/GMCs for each vaccine group. To incorporate possible baseline imbalance among the vaccine groups, an analysis of covariance (ANCOVA) might be performed that incorporate baseline titers/concentrations along with study group and center as factors in the model.

The following SAS code will be used for the ANOVA model:

```
PROC GLM data = dataset;
      class trt center;
      model Ab_post = trt center;
      lsmeans trt / stderr cl tdiff pdiff;
      estimate 'Group A vs. Group B' trt 1 -1;
run;
```

where Ab_post represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, trt indicates the vaccine group, and center the site.

The following SAS code will be used for the ANCOVA model:

```
PROC GLM data = dataset;
      class trt center Ab_pre;
      model Ab_post = trt center Ab_pre;
      lsmeans trt / stderr cl tdiff pdiff;
      estimate 'Group A vs. Group B' trt 1 -1;
run;
```

where Ab_post represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, trt indicates the vaccine group, center the site, and Ab_pre the log-transformed antibody baseline value of the immunogenicity variable.

If the statistical model does not converge due to the factor “centre”, merging some centres or including instead “country” in the model will be considered.

For each *N. meningitidis* serogroup B test strain (M14459, M07-0241084, 96217 and NZ98/254) and each of the serogroups A, C, W and Y, the percentages of subjects with fourfold increase in hSBA titers, and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method [Clopper, 1934] against these strains will be calculated

for each study group at one month after the 1st vaccination and one month after the 2nd vaccination, for serogroup B test strains, and at one month after (study) vaccination of MenACWY, for serogroups A, C, W and Y. The CIs for the rate difference between groups will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

The percentage of subjects with fourfold increase in hSBA titers one month after the 1st and one month after the 2nd vaccination, for serogroup B test strains, and one month after (study) vaccination, for serogroups A, C, W and Y, relative to baseline is defined as:

- If the baseline titer is <limit of detection (LOD), then post-vaccination titer should be ≥ 4x LOD or ≥LLOQ, whichever is greater
- If the baseline titer is ≥LOD but <LLOQ, then post-vaccination titer should be ≥4x LLOQ
- If the baseline titer is ≥LLOQ, then post-vaccination titer should be ≥ 4x the baseline titer

Summary tables will show unadjusted percentages and unadjusted "between-group" differences.

The following table contains the LOD and LLOQ values to be used.

Table 5 LOD, LLOQ and ULOQ values

Serogroups / B strains	LOD*	LLOQ*	ULOQ*
A	5	12	4295
C	4	8	54828
W	4	8	10057
Y	4	10	7624
M14459	4	5	Not defined
96217	6	14	Not defined
NZ298/254	4	6	Not defined
M13520	4	6	Not defined

*Strain, assay cut-off(s) and unit(s) might be subject to change during the course of the study (e.g., in case of requalification, revalidation or standardization). In this case, this will be documented either in a protocol amendment or in the clinical report.

5.5. Analysis of safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

5.5.1.1. Analysis of Solicited Adverse events

All safety analyses will be performed using the Exposed set.

- Frequencies and percentages of subjects experiencing each AE will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic AE overall and at each time point will also be presented.

- Post-vaccination solicited AEs reported from Day 1 (of vaccination) to Day 7 will be summarized for the intervals Day 1-3, Day 4-7, Day 1-7 by maximal severity and by group, excluding the 30-minute measurement, which will be summarized separately. The severity of solicited local AEs, including injection-site erythema, induration and swelling will be summarized according to categories based on linear measurements as presented in Table 6 below.
- Injection site pain and systemic AEs (including fever) occurring up to 7 days after each vaccination will be summarized according to "mild", "moderate" or "severe".
- Each solicited local and systemic AE will also be further summarized as "none" versus "any".
- Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use.
- Body temperature will be summarized by 0.5 °C increments from 38.0 °C/100.4°F up to ≥40 °C/104.0°F and will be broken down accordingly by route of measurement.
- Descriptive statistics (i.e., mean, median, minimum, maximum, low and upper quartiles) of the duration (in days) of solicited local (administration site) and systemic adverse events following each vaccination and overall will be provided by study group and for each solicited reaction.
- Descriptive statistics (i.e., mean, median, minimum, maximum, low and upper quartiles) of day of onset for solicited local (administration site) and systemic adverse reaction following each vaccination and overall will be provided by study group and for each solicited reaction.

Implausible measurements (for further definition see eDiary specification) will be left out of the analysis.

In the event of duplicate solicited AEs being reported both in the study eCRF and the eDiary, the Investigator's assessment will be prioritized for the main analysis.

For participants who have more than one solicited local (i.e., injection site pain, erythema, swelling, induration) or systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) measurement on a day, all data is listed. For the analysis, the worst measurement is analysed. For example, if for a participant a temperature of 38.5°C and 39.0°C is recorded on one day, both values are listed, for the analysis the 39.0°C is analysed.

5.5.1.2. Analysis of eDiary compliance

eDiary compliance will be analysed as follows:

- The average percentage of eDiary entries will be reported by visit and overall, for each study group. The percentages of eDiary entries at subject level will be calculated and listed by visit.
- The numbers and percentages of participants who provided eDiary entries for the solicited local (administration site) and systemic adverse events during the 7 days after each vaccination (including the day of vaccination and excluding the 30-minute measurements) will be presented for each reporting day for each solicited reaction, by study group.
- The numbers and percentages of participants who reported eDiary entries for all the solicited local (administration site) and systemic adverse events, from Day 1 to Day 7 (for all 7 days), after each vaccination (including the day of vaccination and excluding the 30-minute measurements) will be reported by visit and by study group.
- The numbers and percentages of participants who provided eDiary entries for each solicited local (administration site) and systemic adverse events consecutively, for three days (day 1 through day 3 post-vaccination), 5 days (day 1 through day 5 post-vaccination) and 7 days (day 1 through day 7 post-vaccination), will be reported for each solicited reaction by visit and by study group.

Table 6 Intensity scales for solicited symptoms in adults and children of 6 years of age or more

Adolescents (from 11 years of age) and adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Injection Site Induration, Swelling, Erythema	0	1 – 24 mm
	1	25 - 50 mm
	2	51 - 100 mm
	3	>100 mm
Temperature*	0	< 38.0°C (100.4°F)
	1	≥ 38.0 - 38.9°C (100.4 – 102.02°F)
	2	≥ 39.0 - 39.9°C (102.2 – 103.82°F)
	3	≥ 40.0°C (104.0°F)
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Nausea	0	Normal

Adolescents (from 11 years of age) and adults		
Adverse Event	**Intensity grade**	**Parameter**
	1	Mild: Nausea that is easily tolerated
	2	Moderate: Nausea that interferes with normal activity
	3	Severe: Nausea that prevents normal activity
Generalized Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Generalized Arthralgia	0	Normal
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

*Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity for subjects.

Between groups assessment

No statistical tests for between-group comparisons will be performed.

The percentages of subjects with solicited local and systemic AEs during the 7 days (including the day of vaccination) following the first (Visit 1), the second (Visit 3) and the third (Visit 4) vaccination for all groups will be calculated.

Descriptive summary statistics will be provided by obesity status (i.e., BMI <30kg/m2 vs >30.kg/m2).

5.5.1.3. Analysis of Unsolicited Adverse Events

All safety analyses will be performed using the Exposed set.

This analysis applies to all AEs occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE eCRF, with a start date on or after the date of first vaccination. All AEs starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and by interval of study observation. When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events (SAEs)
- Adverse Events of Special Interest (AESIs) for subjects who received rMenB+OMV NZ

- Adverse events that are possibly or probably related to vaccine.
- Adverse event leading to withdrawal with relationship to COVID-19.
- Adverse events leading to a medically attended visit.

The frequencies and percentages of subjects who reported at least one immediate unsolicited adverse event (i.e., reactions that occurred during the first 30 minutes after any vaccination that have been flagged as immediate in the eCRF and have not been reported in the eDiary) following any study vaccination will be reported by study group.

Data listings of all AEs will be provided by subject. In addition, AEs in the categories above will be provided as listed data.

Between groups assessment

No statistical tests for between-group comparisons will be performed.

- The percentages of subjects with any unsolicited AEs (including all SAEs) during the 30 days (including the day of vaccination) following the first (Visit 1), the second (Visit 3) and the third (Visit 4) vaccination for all groups will be calculated.
- The percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, throughout the study period (Day 1 /Month 0 to Month 9) will be calculated. Among subjects who are followed for 12 months after their last dose the percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, between SFU 5/Month 9 and SFU 7/Month 15 will also be calculated.
- The percentages of subjects with AESI throughout the study period (Day 1 /Month 0 to Month 9) will be calculated (for subjects who received rMenB+OMV NZ). Among subjects who are followed for 12 months after their last dose the percentages of subjects with AESI, between SFU 5/Month 9 and SFU 7/Month 15 will also be calculated.

Descriptive summary statistics will be provided by obesity status (i.e., BMI <30kg/m2 vs >30.kg/m2).

5.5.1.4. Additional considerations

For clinicaltrials.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

5.5.2. Concomitant Medication

Medications will be coded using the WHODrug dictionary. The frequencies and percentages of subjects starting concomitant medications after vaccination will be tabulated by vaccine group.

6. ANALYSIS INTERPRETATION

The primary objective is divided in three primary endpoints. The first one regards safety and will be only descriptive. The two other endpoints will be achieved if non-inferiority is demonstrated. Non-inferiority is demonstrated if for each of the four serogroups A, C, W and Y (the four serogroup B test strains: M14459, 96217, NZ98/254 and M07-0241084), the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs is >0.5 for group MenB+MenACWY versus group MenACWY (for group MenB+MenACWY versus group MenB).

6.1. Hypotheses related to primary immunogenicity objectives

The statistical hypotheses and analyses are based on the common assumption that the logarithmically (base of 10) transformed hSBA titers are normally distributed.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY to rMenB+OMV NZ

The null (not non-inferiority) and the alternative (non-inferiority) hypotheses are:

$H_{0,i}^{MenB}: \mu_{A,MenB,i} - \mu_{B,MenB,i} \leq \log_{10}(0.5)$ versus

$H_{1,i}^{MenB}: \mu_{A,MenB,i} - \mu_{B,MenB,i} > \log_{10}(0.5)$,

where i=1,…,4 is an index over the four serogroup B strains M14459, 96217, NZ98/254 and M07-0241084, and $\mu_{A,MenB,i}$ and $\mu_{B,MenB,i}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the i^{th} serogroup B strain at one month after the second vaccination in Groups MenB+MenACWY and MenB respectively.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY to MenACWY

The null (inferiority) and the alternative (non-inferiority) hypotheses are:

$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} \leq \log_{10}(0.5)$ versus

$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} > \log_{10}(0.5)$,

where j=1,…,4 is an index over the four serogroups A, C, W and Y, and $\mu_{A,MenACWY,j}$ and $\mu_{C,MenACWY,j}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the j^{th} MenACWY serogroup at one month after the first vaccination in Groups MenB+MenACWY and MenACWY respectively.

The threshold of $\log_{10}(0.5) = -\log_{10} 2 \approx -0.3$ is the non-inferiority margin.

The 8 hypotheses associated with the primary objective will be tested simultaneously, to control for the type I error rate. The testing of the hypotheses will be done simultaneously on all the strains and serogroups.

6.2. Hypotheses related to secondary immunogenecity objectives

There is a non-inferiority test associated with the concomitant rMenB+OMV NZ with MenACWY to MenACWY using ELISA GMCs.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY to MenACWY

The null (inferiority) and the alternative (non-inferiority) hypotheses are:

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} \leq \log_{10}(0.5) \text{ versus}$$

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} > \log_{10}(0.5),$$

where j=1,…,4 is an index over the four serogroups A, C, W and Y, and $\mu_{A,MenACWY,j}$ and $\mu_{C,MenACWY,j}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the jth MenACWY serogroups at one month after the first vaccination in Groups MenB+MenACWY and MenACWY respectively.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY versus MenACWY alone will be claimed if the null hypotheses are rejected for all four serogroups A, C, W and Y, as measured by ELISA GMCs.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints. CCI [redacted]

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final Analysis (Analysis_E1_01)	Public disclosure, Study report

7.2. Statistical considerations for interim analyses

NA

8. CHANGES FROM PLANNED ANALYSES

The electrochemiluminescence-based (ECL) multiplex assay will be used instead of an Enzyme-Linked Immunosorbent Assay (ELISA) to assess the Geometric Mean Concentration (GMCs) against each of the serogroups A, C, W and Y.

The objectives reported in Section 2 will not be changed to maintain the alignment with the study Protocol. Nevertheless, all the outputs generated for the final analysis will reference the actual assay methodology implemented to obtain the results.

This change will also be documented in the Clinical study Report (CSR) as stated in Appendix 2 Section 12.2 of the Protocol.

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

NA

9.2. Statistical Method

NA

10. ANNEXES

For database studies an annex describing the data extraction including extraction criteria and variables should be added.

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 CRF 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 adverse events

For the collection of solicited adverse events, a solicited adverse event will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

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 days

When age at vaccination is to be displayed in days, it will be calculated as:

Age = date of vaccination minus date of birth

10.1.3.2. Age at vaccination in months

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

DOB = 10JUN2017, Date of vaccination = 09JUL2018 -> Age = 12 months

DOB = 10JUN2017, Date of vaccination = 10JUL2018 -> Age = 13 months

10.1.3.3. 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

10.1.3.4. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

10.1.3.7. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

10.1.3.8. 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

10.1.3.9. Geometric mean titres (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Antibody titres or 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 GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.10. 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).

10.1.3.11. 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 one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited adverse events is derived assuming that the solicited adverse event occurred continuously from the first day to the last day the event was reported, regardless of how many days the event was documented in between (i.e., *end date – start date + 1*).

10.1.3.12. 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 CRF pages.

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

10.1.3.13. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarized, 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 one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (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 are below 10kg where one decimal will be displayed.

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

10.1.4.4. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (GMC) and their confidence limits is shown in the following table:

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

GMT or 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 Miettinen and Nurminen [Miettinen, 1985].

10.1.5.3. Adjusted GMT or GMC ratios

The CI for GMC ratio and adjusted GMT will be obtained using an ANOVA model on the logarithm transformed titers. The ANOVA model will include the vaccine group as the fixed effect (3 groups) and the country effect. The GMC ratio and their 95% CI will be derived by exponential transformation of the corresponding group contrast in the model.

When between-group GMT or 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. It should also be clear whether the model is limited to the data from some groups.

10.1.5.4. Vaccine efficacy

NA

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

11. REFERENCES

Clopper C. J, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. Biometrika. 1934;26:404-13.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. Statistics in Medicine, 1985;4,213-226.