Statistical Analysis Plan Amendment 1

Study ID: 220030

Official Title of Study: A Phase 3b, open-label, multi-center study to assess the immune response and safety of the meningococcal group B vaccine rMenB +OMV NZ when administered to healthy participants aged 10 to 20 years old, who were primed during the first 2 years of life

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TITLE PAGE

Protocol Title:	A Phase 3b, open-label, multi-center study to assess the immune response and safety of the meningococcal group B vaccine rMenB+OMV NZ when administered to healthy participants aged 10 to 20 years old, who were primed during the first 2 years of life
Study Number:	220030
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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	02 April 2025	Protocol (20 January 2025)	Not Applicable	Original version
SAP Amendment 1	14 Jan 2026	Protocol Amendment 1 (29 August 2025)	• Section 3.1: Table 5. List of elimination criteria updated: Exposed Set added and PDs 1A, 1E, 1OT updated. • Section 4.5.1.2: Addition of prioritization of the Investigator's assessment where solicited AEs are reported in both the study eCRF and the eDiary. • Section 6.2.1: Addition of the "unable to measure" option in the eCOA calculation.	• Updates to Section 3.1 (Table 5) reflect revisions to PDs leading to elimination. • Updates to Section 4.5.1.2 clarify the approach to handling solicited adverse events documented in both the eDiary and the investigator eCRF. • Updates to Section 6.2.1 ensure appropriate and transparent handling of missing eCOA data for analysis and reporting.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 220030.

1.1. Objectives, Estimands and Endpoints

Table 1 Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the superiority of the immune response to one booster dose of rMenB+OMV NZ in the primed group*, compared to the first dose in naïve group† against each MenB indicator strain.	• hSBA titers against each MenB indicator strain at Visit 2 (Day 31).
Secondary	
To evaluate the humoral immune response to one booster dose of rMenB+OMV NZ in the primed group*, and first dose of rMenB+OMV NZ in the naïve group†.	• hSBA titers against each MenB indicator strain at Visit 2 (Day 31).
To evaluate the bactericidal activity at baseline in the primed group* and in the naïve group†.	• hSBA titers against each MenB indicator strain at Visit 1 (Day 1).
To evaluate the safety of rMenB+OMV NZ throughout the study period.	• Occurrence of solicited administration site and systemic events within 7 days following the first vaccination. • Occurrence of any unsolicited AEs within 31 days (including the day of injection) following the first vaccination. • Occurrence of AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period (Day 1 to Day 31).
Exploratory	
To evaluate the bactericidal activity at baseline and to evaluate the humoral immune response against serotype A, C, W and Y to 1 dose of rMenB+OMV NZ in the primed group* and in the naïve group†.	hSBA titers against each ACWY serogroup at Visit 1 (Day 1) and at Visit 2 (Day 31).

Abbreviations: AE: Adverse event; AESI: adverse event of special interest; hSBA: human serum bactericidal assay; MenB: meningococcal bacteria belonging to N. meningitis serogroup B; rMenB+OMV NZ: recombinant Meningococcal B with Outer Membrane Vesicle derived from *Neisseria meningitidis* serogroup B strain NZ98/254 (New Zealand strain) Vaccine (*Bexsero*); SAE: Serious adverse event.

*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life.

†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

PRIMARY ESTIMAND

Table 2 Study estimand - primary objective

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Primary Estimand: Superiority of the immune response to one booster dose in the primed group* compared to the first dose in the naïve group†.						
Clinical question of interest: The interest lies in demonstrating the superiority of the immune response to a single booster dose of rMenB+OMV NZ in the primed group compared to the first dose in naïve group against each MenB indicator strain, regardless of ICEs occurrence. A supportive analysis will also be conducted to address the instance in which ICEs had never occurred. **Rationale:** As the interest is in evaluating the superiority of the immune response to one booster dose compared to the first dose in naïve participants, in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used. A supportive analysis is conducted using the hypothetical strategy to evaluate the superiority of the immune response to one booster dose compared to the first dose in naïve participants, in a setting where participants would adhere to the protocol requirements.						
Primary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each MenB indicator strain in primed and naïve group at Visit 2 (Day 31)	• Blood draws occurring outside the protocol-defined visit window. • Errors in first/booster dose vaccine administration: ○ Vaccine temperature excursion ○ Expired vaccine ○ Lower volume of vaccine ○ Other errors lead to vaccine not administered according to the protocol • Administration of a vaccination forbidden by the protocol. • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for the primary immunogenicity endpoint, i.e., the value of the endpoint is used regardless of whether or not the intercurrent event occurs. The hypothetical strategy will be used for the supportive analysis, i.e. ICE will be handled as it had never occurred, data post ICE will not be considered for the analysis of the outcome measure.	• Ratio of GMTs against each MenB indicator strain between the primed and naive group at visit 2 (Day 31).
Abbreviations: GMT: geometric mean titer; hSBA: human serum bactericidal assay; MenB: meningococcal bacteria belonging to N. meningitis serogroup B. *Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life. † Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.						

SECONDARY ESTIMANDS

Table 3 Study estimands - secondary objectives

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Secondary Estimand: Immunogenicity of one booster dose in the primed group*, and first dose in the naïve group†						
Clinical question of interest: The interest lies in assess the immune response to a single booster dose of rMenB+OMV NZ in the primed group* and the first dose in the naïve group† against each MenB indicator strain, regardless of ICEs occurrence. **Rationale:** As the interest is in evaluating the immune response to one booster dose in the primed group and to the first dose in naïve group in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used.						
Secondary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each MenB indicator strain at Visit 2 (Day 31)	• Blood draws occurring outside the protocol-defined visit window. • Errors in first/booster dose vaccine administration: o Vaccine temperature excursion o Expired vaccine o Lower volume of vaccine o Other errors lead to vaccine not administered according to the protocol. • Administration of a vaccination forbidden by the protocol. • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for immunogenicity endpoints, i.e., the value for each of the endpoints is used regardless of whether or not the intercurrent event occurs	• Number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each MenB indicator strain at Visit 2 (Day 31). • Number and percentage of participants with hSBA titers ≥LLOQ against each MenB indicator strain at Visit 2 (Day 31). • Number and percentage of participants with four-fold increase** in hSBA titers at Visit 2 (Day 31) relative to Visit 1 (Day 1). • hSBA GMTs and GMRs at Visit 2 (Day 31) compared to Visit 1 (Day 1) against each MenB indicator strain.

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Secondary Estimand: Bactericidal activity at baseline						
Clinical question of interest: The interest lies in evaluate the bactericidal activity at baseline in the primed group* and in the naïve group† against each MenB indicator strain, regardless of ICEs occurrence. **Rationale:** As the interest is in evaluating the bactericidal activity at baseline in the primed group and in the naïve group in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used.						
Secondary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each MenB indicator strain at Visit 1(Day 1)	• Administration of a vaccination forbidden by the protocol. • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for immunogenicity endpoints, i.e., the value for each of the endpoints is used regardless of whether or not the intercurrent event occurs	• Number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each MenB indicator strain, at Visit 1 (Day 1). • Number and percentage of participants with hSBA titers ≥LLOQ against each MenB indicator strain, at Visit 1 (Day 1). • hSBA GMTs against each MenB indicator strain at Visit 1 (Day 1).

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Secondary Estimand: Safety						
Clinical question of interest: The interest is to evaluate the safety of rMenB+OMV NZ throughout the study period. **Rationale:** As the interest is in evaluating the safety of one dose of rMenB+OMV NZ, in a real world setting where participant may not adhere to all the protocol requirements, considering all participants that are exposed to the study vaccine, the treatment policy strategy is used.						
Secondary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	• Occurrence of solicited administration site and systemic events within 7 days following the first vaccination at Day 1 (Visit 1). • Occurrence of any unsolicited AEs within 31 days (including the day of injection) following the first vaccination at Day 1 (Visit 1). • Occurrence of AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period (from Day 1 to Day 31).	• Administration of a vaccination forbidden by the protocol. • Use of a medication forbidden by the protocol. • Errors in first/booster dose vaccine administration: o Vaccine temperature excursion o Expired vaccine o Lower volume of vaccine o Other errors lead to vaccine not administered according to the protocol	A treatment policy strategy will be used for safety endpoints, i.e., the value for each of the safety endpoints is used regardless of whether or not the intercurrent event occurs.	• Percentage of participants reporting solicited administration site and systemic events within 7 days following the vaccination at Visit 1 (Day 1). • Percentage of participants with any unsolicited AEs within 31 days (including the day of injection) following the vaccination at Visit 1 (Day 1). • Percentage of participants reporting AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; GMR: geometric mean ratio; GMT: geometric mean titer; hSBA: human serum bactericidal assay; ICE: intercurrent event; LOD: limit of detection; LLOQ: lower limit of quantification; MenB: meningococcal bacteria belonging to N. meningitis serogroup B; SAE: serious adverse event. *Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life. †Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants. ** Four-fold increase (seroconversion) defined as: • Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2; • Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥2.						

Table 4 Study estimand - exploratory objective

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Exploratory Estimand: The humoral immune response against serotype A, C, W and Y after 1 dose of rMenB+OMV NZ in the primed group* and in the naïve group†						
Clinical question of interest: The interest lies in assess the immune response against serotype A, C, W and Y to 1 dose of rMenB+OMV NZ in the primed group* and in the naïve group†, regardless of ICEs occurrence. **Rationale**: As the interest is in evaluating the bactericidal activity at baseline and evaluating the immune response against serotype A, C, W and Y to one booster dose in the primed group and to the first dose in the naïve group, in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used.						
Exploratory	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB+ OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each ACWY serogroup at Visit 1 (Day 1) and Visit 2 (Day 31)	• Blood draws occurring outside the protocol-defined visit window. • Errors in first/booster dose vaccine administration: o Vaccine temperature excursion o Expired vaccine o Lower volume of vaccine o Other errors lead to vaccine not administered according to the protocol • Administration of a vaccination forbidden by the protocol • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for immunogenicity endpoints, i.e., the value for each of the endpoints is used regardless of whether or not the intercurrent event occurs.	• Number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each ACWY serogroup at Visit 1 (Day 1) and Visit 2 (Day 31). • Number and percentage of participants with hSBA titers ≥LLOQ against each ACWY serogroup at Visit 1 (Day 1) and Visit 2 (Day 31). • Percentage of participants with four-fold increase** in hSBA titers against each ACWY serogroup at Visit 2 (Day 31) relative to Visit 1 (Day 1). • hSBA GMTs and GMRs against each ACWY serogroup at Visit 2 (Day 31) relative to Visit 1 (Day 1).

Abbreviations: GMR: geometric mean ratio; GMT: geometric mean titer; hSBA: human serum bactericidal assay; ICE: intercurrent event; LOD: limit of detection; LLOQ: lower limit of quantification; MenB: meningococcal bacteria belonging to N. meningitis serogroup B.

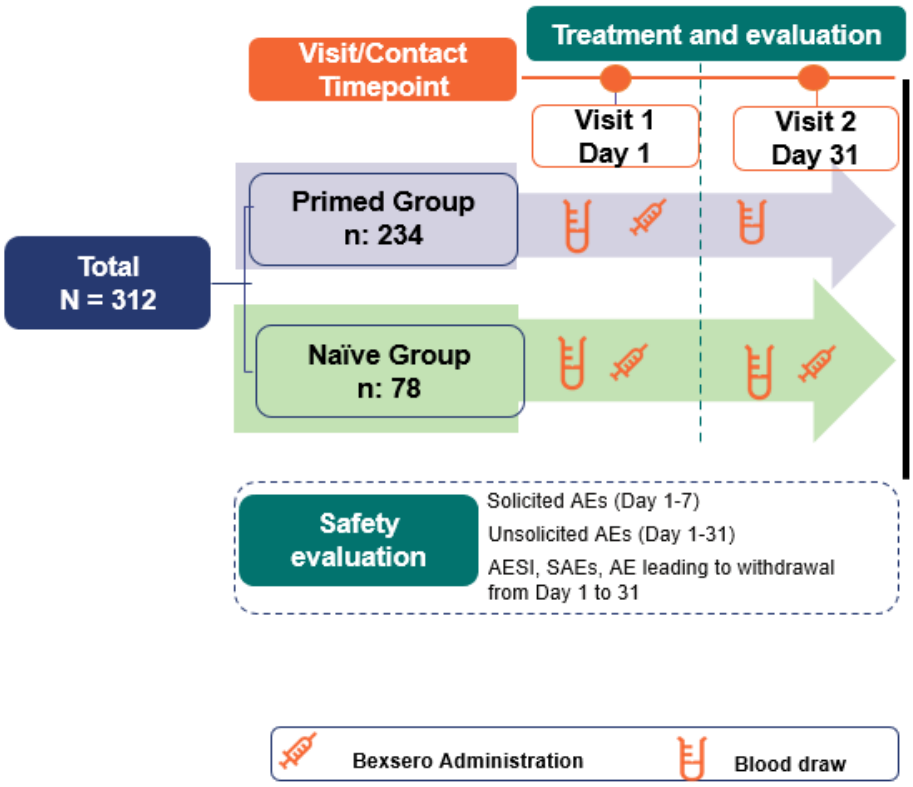
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life.

† Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

** Four-fold increase (seroconversion) defined as:

- Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2;
- Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥ 2.

1.2. Study Design

Overview of Study Design and Key Features	
Figure 1 Study design overview  Abbreviations: AESI = Adverse event of special interest; N/n = Number of participants; (S)AE = (Serious) Adverse event.	
Design Features	This is a Phase 3b, open-label, multi-center study to assess the immune response and safety of a single booster dose of rMenB+OMV NZ when administered to healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in a 2+1 or 3+1 schedule during the first 2 years of life. The study will include 2 groups (see Figure 1): • Primed group (n=234): participants who were primed with rMenB+OMV NZ in 2+1 or 3+1 schedule during the first 2 years of life in studies V72_28, V72_P12E1, V72_P13E1 or in routine practice will receive 1 dose of rMenB+OMV NZ. • Naïve group (n=78): participants who are group B-meningococcal-vaccine-naïve within the same age range as the primed group will be recruited and will receive 2 doses of rMenB+OMV NZ, 1 month apart (with 30 days of interval). Participants will be monitored for safety throughout the study period. For each participant enrolled the duration will be approximately 1 month.

Overview of Study Design and Key Features	
Study intervention	Study intervention is provided as a suspension for injection in a pre-filled syringe and will be administered at a dosage of 0.5 ml at each vaccine administration. Please refer to the current SmPC for information for data supporting the dose, dose volume, formulation, dosing frequency, safety and route of administration that are proposed for the clinical use of rMenB+OMV NZ. Study intervention will be dispensed and administered at the study visits as summarized in the SoA.
Study intervention Assignment	Participants will be recruited in a 3:1 ratio in the Primed group and the Naïve group. Due to the reason that the participants recruited in each group are distinct group of population, a sequential list will be used in RTMS for intervention allocation at Visit 1 (Day 1) and Visit 2 (Day 31). Participants will be assigned with a unique number (sequential number) in ascending numerical order at each study site. The sequential number encodes the participant's assignment to one of the two arms of the study, according to the-sequential schedule generated prior to the study by the statistics department at GSK sponsor. To ensure balanced representation across age demographics, at least 20% of the total subjects per arm will be represented within each specified age group: 10-15 years and 16-20 years of age.
Interim Analysis	Not applicable.

2. STATISTICAL HYPOTHESES

The primary objective is planned to be addressed using formal hypothesis testing.

The primary aim of the study is to demonstrate the superiority of the immune response to one booster dose of rMenB+OMV NZ in the primed group, compared to the first dose in the naïve group against each MenB indicator strain.

For the primary estimand, the following 1-sided hypotheses are planned to be tested simultaneously against each of the four MenB indicator strains, considering a 1-sided type-I error of 2.5%.

Let π_k be defined as the ratio between the GMT in the primed group and the GMT in the naïve group at 1 month following the booster or first dose for each of the strains, and k = 1,2,3,4 represents the specific indicator strain (M14459, 96217, NZ98/254, and M13520).

$H_{0k}: \pi_k \leq 1$ *vs.* $H_{1k}: \pi_k > 1$

The null hypothesis will be rejected (i.e., superiority demonstrated) if the lower limit of the two-sided 95% confidence interval (CI) of the ratio of the GMTs is greater than 1. The study will be claimed a success if each of the 4 single hypotheses is rejected simultaneously.

2.1. Multiplicity Adjustment

No multiplicity adjustment will be performed for any of the endpoints.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who entered the study (who were assigned with the subject ID or received study vaccine or underwent a post screening study procedure). Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Exposed	All participants who entered the study and received at least 1 dose of study vaccine.	Study Population and Safety
Persistence Analysis Set (PAS)	All participants who entered the study and have immunogenicity data at baseline.	Persistence
Full Analysis Set (FAS)	All participants who received at least 1 dose of study vaccine and have post-vaccination immunogenicity data.	Immunogenicity
Supportive Immunogenicity Analysis Set (SIAS)	All participants who received at least 1 dose of study vaccine who comply with the procedures and intervals defined in the protocol, who did not present with a medical condition leading to exclusion, have the blood collection within an appropriate window; have available data concerning immunogenicity endpoint measures and have no other major protocol deviations.	Immunogenicity

3.1. Criteria for eliminating data from Analysis Sets

The following criteria will be used to identify participants to be eliminated from analysis. Details are provided below (see Table 5) for Exposed Set, FAS, Persistence and Supportive Immunogenicity Analysis Sets.

Table 5 List of elimination criteria

Protocol Deviation Category	Protocol Deviation Sub-Category	Timepoints where the criteria are checked	Applicable for analysis set/endpoint				
			Enrolled Set	Exposed Set	Persistence Analysis Set	Full Analysis Set	Supportive Immuno Analysis Set*
Informed Consent and Process	1A. Signed informed consent and assent (when applicable) not available on site	All	All	All	All	All	All
	1B. Wrong informed consent and/or assent version signed	All	None	None	None	None	None

Protocol Deviation Category	Protocol Deviation Sub-Category	Timepoints where the criteria are checked	Applicable for analysis set/endpoint				
			Enrolled Set	Exposed Set	Persistence Analysis Set	Full Analysis Set	Supportive Immuno Analysis Set*
	1C. Informed consent and/or assent not signed and/or dated by subject (parent/Legally Acceptable representative, if applicable)	All	All	All	All	All	All
	1D. Informed consent and/or assent not signed and/or dated by appropriate site staff	All	All	All	All	All	All
	1E. Informed consent and/or assent not signed prior to any study procedure	All	None	None	None	None	All
	1OT. other informed consent and/or assent deviation	All	None	None	None	None	None
	3C - Not withdrawn from study after withdrawing the consent and assent (when applicable)	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	All
Inclusion Criteria	2A. Inclusion Criteria not met	Visit 1	None	None	None	None	All
Exclusion Criteria	2B. Exclusion Criteria Met	Visit 1	None	None	None	None	All
Concomitant Medication	4A. Medication, excluded by the protocol, was administered	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	All
	4B. Vaccine, excluded by the protocol, was administered	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	All
Laboratory Assessment	8G. Biological sample specimen procedures	Visit 1	None	None	None	None	Visit 1
		Visit 2	None	None	None	None	Visit 2
	6A. Missed Assessment	Visit 1	None	None	All	None	Visit 1
		Visit 2	None	None	None	All	All
	6D. Out of Window assessment	Visit 2	None	None	None	None	Visit 2
Randomization	8A. Enrollment procedure (subject assigned to wrong stratum, subject enrolled out of order)	Visit 1	None	None	None	None	All

Protocol Deviation Category	Protocol Deviation Sub-Category	Timepoints where the criteria are checked	Applicable for analysis set/endpoint				
			Enrolled Set	Exposed Set	Persistence Analysis Set	Full Analysis Set	Supportive Immuno Analysis Set*
Visit Schedule	5A. Missed visit	Visit 2	None	None	None	All	All
	5B. Out of window visit	Visit 2	None	None	None	None	Visit 2
IP Conditions	7E. Use of study treatment impacted by a temperature excursion which was not reported or approved, or which was disapproved for further use	Visit 1	None	None	None	None	Visit 1
		Visit 2	None	None	None	None	Visit 2
IP Preparation	7F. Study treatment not prepared as per protocol (e.g. reconstitution)	Visit 1	None	None	None	None	Visit 1
		Visit 2	None	None	None	None	Visit 2
IP Administration	7A. Study treatment not administered per eligibility criteria	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	Visit 2
	7C. Wrong study treatment or assignment administered	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	Visit 2
	7D. Expired study treatment administered	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	Visit 2
	7G. Study treatment not available at site for administration	Visit 1	None	All	None	All	All
		Visit 2	None	None	None	None	Visit 2
	7H. incorrect volume given	Visit 1	None	None	None	None	Visit 1
		Visit 2	None	None	None	None	Visit 2
	7M. Incorrect administration of IP	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	Visit 2
	7OT. Other deviations related to wrong study treatment/administration/dose	Visit 1	None	None	None	None	All
		Visit 2	None	None	None	None	Visit 2
	6G. Out of Window – Treatment administration	Visit 2	None	None	None	None	Visit 2
Efficacy	7B. Study treatment administered while contraindication	Visit 1	None	None	None	None	Visit 1
		Visit 2	None	None	None	None	Visit 2
		Visit 1	None	None	None	None	Visit 1

Protocol Deviation Category	Protocol Deviation Sub-Category	Timepoints where the criteria are checked	Applicable for analysis set/endpoint				
			Enrolled Set	Exposed Set	Persistence Analysis Set	Full Analysis Set	Supportive Immuno Analysis Set*
	3A. Not withdrawn from study after developing withdrawal criteria	Visit 2	None	None	None	None	Visit 2
Subject Discontinuation	3B. Not discontinued from study treatment	Visit 1	None	None	None	None	Visit 1
		Visit 2	None	None	None	None	Visit 2
Administrative	10A. Fraudulent Data	All	All	All	All	All	All

4. STATISTICAL ANALYSES

4.1. General Considerations

The immunogenicity primary and secondary objectives and the exploratory analysis will be conducted on the Full Analysis Set. The persistence secondary objectives will be conducted on the Persistence Analysis Set and the safety analysis will be based on the Exposed set. The supportive analysis will be conducted on the Supportive Immunogenicity Analysis Set.

4.1.1. General Methodology

Participants who withdraw from the study will not be replaced.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Continuous data will be summarized using descriptive statistics: N, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value (Visit 1, Day 1). If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed. In this case, baseline, and baseline-derived values (e.g., change from baseline) will be set to missing.

4.2. Primary Endpoint(s) Analyses

The analysis for the immunogenicity primary endpoint will be based on the FAS. Additionally, a supportive analysis will be conducted using the Supportive Immunogenicity Analysis Set (SIAS).

4.2.1. Definition of endpoint(s)

For the definition of the primary endpoint, please refer to Table 2.

4.2.2. Main analytical approach

Objective	Analysis
To demonstrate the superiority of the immune response to one booster dose of rMenB + OMV NZ in the primed group*, compared to the first dose in the naïve group† against each MenB indicator strain.	**Analysis set:** Full Analysis Set **Statistical Methods:** The hSBA titers at 1 month after the first or booster dose (Visit 2, Day 31) will be logarithmically transformed (base10) to fulfill the normal distribution assumption. For each MenB indicator strain the GMTs for the primed* and the naïve† group will be obtained from an ANOVA and then exponentiating the log-transformed means and their 95% CIs. The ratio of the GMTs between the primed* and naïve† group and the corresponding 95% CIs will be calculated exponentiating the difference of the log-transformed means and the lower and upper limits of the 95% CIs on the difference obtained from the ANOVA model above. The null hypothesis will be rejected if the lower limit of the 95% confidence interval of the ratio of the GMTs is >1.

CI: confidence interval; LL: lower limit; MenB: meningococcal bacteria belonging to serogroup B.
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

4.2.3. Sensitivity analysis

To assess the robustness of the results of the primary analysis, causal inference methods will be applied. Specifically, propensity score (PS) weighting methods will be used for balancing observed covariates between primed and naïve groups [Li, 2018]. In this study, the PS is defined as the probability of being in the primed group, conditional on the observed covariates. It is a balancing score in that, given the PS, the distributions of observed covariates between groups are similar [Rosenbaum, 1983].

One common PS weighting method is Inverse Probability Weighting (IPW). This method involves weighting the outcome of each participant in the primed group by the inverse of their probability of being primed (i.e., the inverse of the PS), and the outcome of each participant in the naïve group with the inverse of their probability of being naïve. Note that the PS score is unknown and needs to be estimated. To this scope, a logistic model will be used, where the response variable is a binary indicator for membership in the primed group.

Under the Stable Unit Treatment Value Assumption [Rubin, 1980] and Strong Ignorability [Rosenbaum, 1983]– along with a correctly specified PS model— a consistent estimator of average causal effect of interest, namely, the ratio of the GMT in the primed group and in the naïve group, can be obtained by (i) computing the weighted average of the logarithmically transformed (base10) outcomes in the primed and naïve groups; (ii) exponentiating (10 to) the difference in these weighted averages. This IPW estimator will be augmented with regression models for the endpoint variable in order to improve efficiency of the estimation – a formal definition of the augmented estimator can be found in Mao et al. [Mao, 2019]. The Augmented IPW (AIPW) estimator is doubly robust: it is consistent for the average causal effect of interest as long as either the model for the endpoint variable or the propensity score model is correctly specified [Ding, 2018].

Two Figures pertaining to this sensitivity analysis will be produced.

1. A plot of the Absolute Standardized Differences (ASDs) in the observed covariates by group (primed and naïve), before and after weighting. A formal definition of ASDs for the general family of balancing weights can be found in Li & Li [Li, 2019a]. ASDs below 0.1 will be considered indicative of negligible imbalance. This threshold is the rule-of-thumb in the literature.
2. A plot showing the PS distributions by group (primed and naïve). Poor overlap between these distributions can result in extremely large weights, which would increase the variability of the estimated effect. In that case, trimming or alternative PS-based methods, e.g., Overlap Weights [Li, 2019b], will be considered to obtain more reliable results.

The R package “PSweight” (version 1.2.0) will be used to implement the method [Zhou, 2022]. The variance will be calculated by nonparametric bootstrap. At each b bootstrap iteration ($b = 1, \dots, B$), both the propensity score and outcome models will be re-fitted.

4.2.4. Additional estimands

4.2.4.1. Supportive analysis

Objective	Analysis
To demonstrate the superiority of the immune response to one booster dose of rMenB + OMV NZ in the primed group*, compared to the first dose in the naïve group† against each MenB indicator strain.	**Analysis set:** Supportive Immunogenicity Analysis Set **Statistical Methods:** The hSBA titers at 1 month after the first or booster dose (Visit 2, Day 31) will be logarithmically transformed (base10) to fulfill the normal distribution assumption. For each MenB indicator strain the GMTs for the primed* and the naïve† group will be obtained from an ANOVA and then exponentiating the log-transformed means and their 95% CIs. The ratio of the GMTs between the primed* and naïve† group and the corresponding 95% CIs will be calculated exponentiating the difference of the log-transformed means and the lower and upper limits of the 95% CIs on the difference obtained from the ANOVA model above.

CI: confidence interval; MenB: meningococcal bacteria belonging to serogroup B.
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Definition of endpoints

For the definition of the secondary endpoints, please refer to Table 3.

4.3.2. Main analytical approach

Objective	Analysis
To evaluate the humoral immune response to one booster dose of rMenB+OMV NZ in the primed group*, compared to the first dose in naïve group† against each MenB indicator strain.	**Analysis set:** Full Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each MenB indicator strains and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be determined at 1 month after booster or first dose (Visit 2, Day 31) [Clopper, 1934]. Between group difference (primed group vs naïve group) at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥LLOQ against each MenB indicator strain and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be determined at 1 month after booster or first dose (Visit 2, Day 31).

Objective	Analysis
	Between group difference (primed group vs naïve group) at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The number and percentage of participants with four-fold increase** in hSBA titers at 1 month after booster or first dose (Visit 2, Day 31) relative to baseline (Visit 1, Day 1) and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated against each MenB indicator strain. Between group difference (primed group vs naïve group) at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The hSBA GMTs and GMRs at 1 month after booster or first dose (Visit 2, Day 31) compared to Visit 1 (Day 1) will be calculated against each MenB indicator strain.
To evaluate the bactericidal activity at baseline in the primed group* and in the naïve group†.	**Analysis set:** Persistence Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated against each MenB indicator strain at baseline (Visit 1, Day 1). Between group difference (primed group vs naïve group) at baseline will be calculated, as well as their associated 95% CIs.
	Analysis set: Persistence Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥LLOQ and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated against each MenB indicator strain at baseline (Visit 1, Day 1). Between group difference (primed group vs naïve group) at baseline will be calculated, as well as their associated 95% CIs.
	Analysis set: Persistence Analysis Set **Statistical Methods**: The hSBA GMTs will be calculated against each MenB indicator strain at Visit 1 (Day 1). GMTs ratio between the primed group the naïve group at baseline will be calculated, as well as their associated 95% CIs.

CI: confidence interval; MenB: meningococcal bacteria belonging to serogroup B.
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.
** Four-fold increase (seroconversion) defined as:

- Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2;
- Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥2.

4.4. Exploratory Endpoint(s) Analyses

4.4.1. Definition of endpoints

For the definition of the exploratory endpoints, please refer to Table 4.

4.4.2. Main analytical approach

The analyses of the exploratory endpoints will be conducted on the Full Analysis Set.

Objective	Analysis
To evaluate the bactericidal activity at baseline and to evaluate the humoral immune response against serotype A, C, W and Y to 1 dose of rMenB + OMV NZ in the primed group* and in the naïve group†	**Analysis set:** Full Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each ACWY serogroup and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be determined at baseline (Visit 1, Day 1) and at 1 month after booster or first dose (Visit 2, Day 31). Between group difference (primed group vs naïve group) at baseline and at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥LLOQ against each ACWY serogroup and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be determined at baseline (Visit 1, Day 1) and at 1 month after booster or first dose (Visit 2, Day 31). Between group difference (primed group vs naïve group) at baseline and at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The number and percentage of participants with four-fold increase** in hSBA titers at 1 month after booster or first dose (Visit 2, Day 31) relative to baseline (Visit 1, Day 1) and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated against each ACWY serogroup. Between group difference (primed group vs naïve group) at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The hSBA GMTs and GMRs at 1 month after booster or first dose (Visit 2, Day 31) compared to Visit 1 (Day 1) will be calculated against each ACWY serogroup.

CI: confidence interval; MenB: meningococcal bacteria belonging to serogroup B.
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.
** Four-fold increase (seroconversion) defined as:

- Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2;
- Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥2.

4.5. Safety Analyses

4.5.1. Definition of endpoints

For the definition of the safety endpoints, please refer to Table 3.

4.5.2. Main analytical approach

The safety analyses will be based on the Exposed Set, unless otherwise specified.

Objective	Analysis
To evaluate the safety of rMenB+OMV NZ throughout the study period.	**Analysis set:** Exposed **Statistical Methods**: The number and percentage of participants reporting solicited administration site and systemic events within 7 days (including the day of injection) following the first vaccination at Visit1, (Day 1) will be presented. All solicited events will be summarized according to defined severity grading scales. Number and percentages of participants experiencing each event will be presented for each symptom severity. Post-vaccination solicited events reported from Day 1 to Day 7 will be summarized by maximal severity and by vaccine group, excluding the 30-minutes measurement, which will be summarized separately. The severity of solicited administration site events will be summarized. Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of participants reporting use.
	Analysis set: Exposed **Statistical Methods**: The number and percentage of participants with any unsolicited AEs within 31 days (including the day of injection) following the first vaccination at Visit 1 (Day 1) will be presented. The number and percentage of participants reporting AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period (Day 1 to Day 31) will be presented. This analysis applies to all AEs occurring during the study, judged either as 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. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. All AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class and preferred term within system organ class. These summaries will be presented by vaccine group and by interval of study observation. When an AE occurs more than once for a participant, the maximal severity and strongest relationship to the vaccine group will be counted.

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

AE: adverse event; AESI: adverse event of special interest; CI: confidence interval; GMT: geometric mean titer; GMR: geometric mean ratio; LOD: limit of detection; LLOQ: lower limit of quantification; MenB: meningococcal bacteria belonging to serogroup B; SAE: serious adverse event;
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

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, nausea, fatigue, myalgia, arthralgia, headache) measurement on a day, the event with greater severity is analyzed. 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 analyzed.

4.5.3. Extent of Exposure

A summary of the number and percentage of participants receiving the first (i.e., only the first) and the second doses will be provided on the Exposed Set.

4.5.4. Additional Safety Assessments (if applicable)

4.5.4.1. Vital Signs

Vital signs are only recorded at Visit 1 and will only be listed.

4.6. Other Analyses

4.6.1. Subgroup analyses

Subgroup analyses may be conducted by age group (10-15 years and 16-20 years) for the primary analysis, employing the statistical methods outlined in Section 4.2.2.

Month and year of birth are collected to stratify the population, enabling to assess the superiority of the immune response to a single booster dose in the primed group compared to the first dose in the naïve group across different age group for each MenB indicator strain. For each MenB indicator strain, the GMT ratios between the primed and naïve groups will be calculated, along with their 95% confidence intervals, for each age group.

Additionally, the number and percentage of participants achieving a four-fold increase in hSBA titers one month post-booster or first dose (Visit 2, Day 31) relative to baseline (Visit 1, Day 1) will be determined for each age group. The corresponding exact two-sided 95% confidence intervals will be calculated using the Clopper-Pearson method. The difference between the groups (primed vs. naïve) at one month after the booster or first dose, along with their associated 95% CIs, will be calculated for each age group.

4.7. Interim Analyses

Not applicable.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 20 January 2025).

5. SAMPLE SIZE DETERMINATION

To demonstrate the superiority of the humoral immune response to one booster dose of rMenB+OMV NZ vaccine administered to participants aged 10 to 20 years that were primed in their early life, compared to the first dose in naïve group, the following hypothesis will be tested simultaneously against each of the four MenB indicator strains:

Null hypothesis vs. alternative hypothesis:

$H_{0k}: \pi_k \leq 1$ *vs.* $H_{1k}: \pi_k > 1$,

where k = 1,2,3,4 corresponds to the 4 indicator strains (M14459, 96217, NZ98/254, and M13520) and π_k represents the ratio between the GMT in the primed group and the GMT in the naïve group at 1 month following the booster or first dose for each of the strains.

The null hypothesis will be rejected (i.e., superiority demonstrated) if the lower limit of the two-sided 95% confidence interval (CI) of the ratio of the GMTs is greater than 1. The study will be claimed a success if each of the 4 single hypotheses are rejected simultaneously.

Table 6 shows the power to demonstrate the superiority of the humoral immune response to an additional booster dose of rMenB+OMV NZ vaccine compared to the first dose in naïve group. i.e., the lower limit of the two-sided 95% CI of the ratio of the GMTs at 1 month after the booster or first dose of the rMenB+OMV NZ vaccine is greater than 1. Assumptions on the actual ratio were taken from V72_75 trial [Santolaya, 2012] considering participants from group 3b (V72P10), as the trial designs and age groups considered are the one closest to the current study. It is assumed that the participants in the current study will have antibody responses similar to those observed in those previous study.

With a sample size of 280 evaluable participants using a two sample T-test assuming equal variance, given a one-sided type I error level of 2.5% for each test, the probability to reject the null hypothesis when it is false (power) is 91.3%, 99.9%, 100% respectively for strains M13520 (NHBA), NZ98/254 (PorA) and both M14459(fHbp) and 96217 (NadA) strains. The overall power is 91.2%, the product of the 4 individual strain powers. With an assumed 10% of non-evaluable participants a and a 3:1 participant ratio between group, the number of participants to be enrolled will be 312, 234 in the primed group and 78 in the naïve group.

The purpose of this study is to establish the immunogenicity and safety of a single booster dose in adolescents, as such a sufficient enrolment is needed in the primed group for this purpose. Participants in the control group are enrolled to provide immunogenicity and safety for comparison, while the safety, tolerability and immunogenicity of a 2-dose schedule of Bexsero in adolescents and young adults is well-established. Furthermore, considering that the study will also be conducted in countries where Bexsero is part of the infant NIP, there could be difficulty in finding naïve subjects, and a 3:1 ratio will improve the study feasibility.

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Study populations are specified in Section 3. together with the related analyses.

A summary of the number of participants in each of the participant level analysis set will be provided.

Consort tables, providing subject eliminations and withdrawals from one global study population to another one, will be provided for:

- Exposed Set to Full Analysis Set;
- Exposed Set to Persistence Analysis Set;
- Full Analysis Set to Supportive Immunogenicity Analysis Set;

In case the Enrolled Set is different from the Exposed Set, an additional consort table from Enrolled Set to Exposed Set will be added.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided based on the enrolled set. Additionally, reasons for study withdrawal will be summarized.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age at first vaccination, age group (10-15 years of age, 16-20 years of age), gender, country, site, ethnicity and race will be summarized with descriptive statistics. These summaries will be provided for Enrolled Set, Exposed Set, Full Analysis Set and Persistence Analysis Set.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study, following IQVIA's Standard Operating Procedures (SOP). These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorized in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations leading to exclusion from the analyses will also be summarized.

The number of participants enrolled into the study as well as the number of participants excluded from each analysis set will be tabulated.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using WHO Drug dictionary.

Prior and concomitant medications and vaccinations will be summarized separately and listed by vaccine group on Exposed Set.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.

- Dosage information including dose and frequency.

The number and percentage of participants using concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) at any point during Visit 1 to Visit 2 will be summarized.

6.1.5. Medical and vaccination history

Medical/vaccination history, pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention will be summarized on the Exposed Set by study group respectively.

6.1.6. Study Intervention Compliance

A summary of the number and percentage of participants receiving the first (i.e., only the first) and the second doses by study group will be provided on the Exposed Set.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

6.2.1. eDiary Compliance

The study protocol specifies a 7-day period for recording solicited AEs, during which eDiary entries completed by the participants are evaluated to determine the eCOA compliance at the study level.

The eCOA compliance is defined as the total number of collected daily eDiary entries over the total number of expected daily eDiary entries. Overall eDiary compliance (Day 1 to 7) is calculated as:

$$\frac{Total\ number\ of\ complete\ daily\ eDiaries}{Expected\ number\ of\ complete\ daily\ eDiaries} \times 100$$

An eDiary is considered complete for a given day if there is no missing data within that day. An explicit “unable to measure” response is treated as a valid and complete entry for that item and therefore is not classified as missing data. The eDiary compliance will be reported overall and for each study group.

For each subject the percentage of eDiary entries during the 7-day solicited period will be calculated. The average of the percentages of eDiary entries calculated at subject level will be reported, for each study group.

Additionally, for each day (from Day 1 to Day 7), the number and percentage of completed eDiaries will be summarized by study group using a frequency table. The denominator will be the number of expected completed eDiaries (i.e., the number of participants).

Monitoring of eDiary compliance will be done as follows:

eDiary compliance targets are defined based on Quality Tolerance Limits (QTLs) that are reviewed on a regular basis, according to the IQVIA's template. These QTLs are based on the same metric used for the aforementioned analysis, and no additional compliance criteria were established for this study.

Based on QTL definition:

- An overall (Day 1 to 7) eDiary compliance around 80% is considered acceptable.

6.3. Appendix 3 Data Derivations Rule

This section contains standard rules for data display and derivation for clinical and epidemiological studies.

6.3.1. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

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.

6.3.2. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset. • 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 15th ▪ A missing day and month will be replaced by June 30th

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:<table>
<tr><td>Missing start day</td><td>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.</td></tr>
<tr><td>Missing start day and month</td><td>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.</td></tr>
<tr><td>Missing end day or day and month</td><td>When end day is missing then impute as 15th of month. When day and month are missing, then impute as June 30th. If imputed end date is before start date then set it to start date.</td></tr>
<tr><td>Others</td><td>All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.</td></tr>
</table></td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the same convention used for adverse events.</td></tr>
<tr><td>Age</td><td>Birth dates will be imputed using the following conventions:
▪ A missing day will be replaced by 15
▪ A missing month will be replaced by June 30th</td></tr>
</table>

6.3.3. Data derivation

6.3.3.1. 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

6.3.3.2. 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. For each MenB indicator strain, GMTs for both primed* and naïve† groups will be derived using an ANOVA, with age and country as covariates. 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.

6.3.4. Statistical methodology

6.3.4.1. Exact confidence intervals around proportions

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

6.3.4.2. 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].

6.3.5. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
Bexsero	

7. REFERENCES

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