SAP Core Body

Title: A descriptive, Phase IV, open-label, single-arm multi-center study to assess the immunogenicity and safety of MenQuadfi® as a booster vaccine in healthy toddlers 12 to 23 months of age who had been primed with at least 1 dose of another quadrivalent meningococcal conjugate vaccine, ie, Nimenrix® (MCV4-TT) or Menveo® (MCV4-CRM), in infancy.

Study Code: MEQ00086

Study Phase: Phase IV

SAP Core Body Version: 1.0

SAP Core Body Date: 04 March 2025

Protocol Version Number: 2.0

The SAP Code Body should be used in conjunction with the study protocol and the SAP TLF.

Version History

Not applicable as this is the first version of the SAP Core Body.

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1 Overall Design

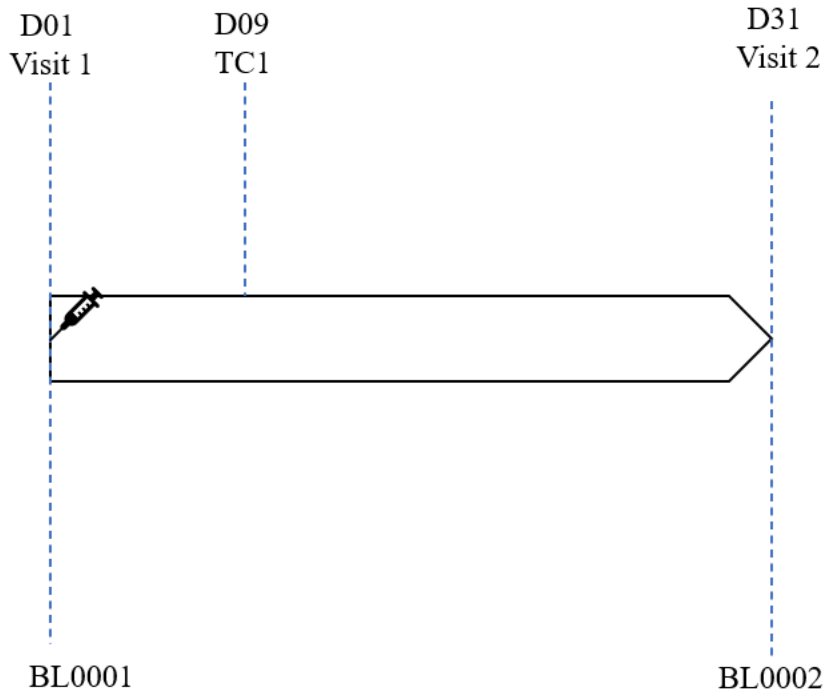
The design of the study is summarized in Table 1.1.

Table 1.1: Overall Design

Type of design	Open-label, single-group, multi-center
Phase	IV
Control method	Un-controlled
Study population	Healthy toddlers aged 12 months to 23 months
Level and method of blinding	Open-label
Study intervention assignment method	No randomization
Number of participants	A total of approximately 180 participants (minimum of 30 evaluable participants from the low - enrolling of the 2 priming vaccines) are expected to be enrolled with the aim to obtain a total of 150 evaluable participants.
Intervention groups	All eligible participants (12 – 23-month-old toddlers who had received at least one of two priming doses of either Nimenrix® or Menveo® vaccine during infancy as part of their recommended immunization, before 12 months of age) will be assigned in an open-label design to receive a single booster dose of the MenACYW conjugate vaccine with an interval of at least 2 months after the last vaccination with Nimenrix® or Menveo®, as an intramuscular (IM) injection at D01.
Total duration of study participation	The duration of each participation will be approximately 1 month for each participant
Countries	Argentina
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

The study design of MEQ00086 study is presented in Figure 1.1.

Figure 1.1: Graphical study design



BL: blood sample
BL0001 (pre-vaccination) and BL0002 for immunogenicity assessments

D: day; TC: telephone call;

D09 TC1: Day 09 safety follow up

: Vaccination

The schedule of activities are given in Table 1.2

Table 1.2: Schedule of activities

Phase IV Study, 2 Visits, 1 Vaccination, 2 Blood Samples, ~1 Month Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	TC1§	Visit 2**
Study timelines (days)		D01	D09	D31
Time windows (days)		NA	[+2 D]	[+14 D]
Visit procedures:				
Informed consent	X	X		
Inclusion/exclusion criteria	X	X		
Collection of demographic data	X	X		
Collection of Medical history	X Significant Medical History	X		
Collection of vaccination history	X	X		
Physical examination		X		X
Pre-vaccination temperature		X		
Review of temporary contraindications for blood sampling*	X	X		X
Allocation of participant number	X	X		
Blood sampling (BL)† [5 mL]	X	BL0001 Pre-vac		BL0002
Vaccination (vac)	X	X		
Immediate surveillance (30 min)	X	X		
Diary card provided		X		
Collection of solicited injection site and systemic reactions	X	X	X	
Collection of unsolicited adverse events (AEs)	X	X	X	X
Diary card collected				X
Collection of concomitant medications	X Reportable concomitant medication	X	X	X
Collection of SAEs, including adverse events of special interest (AESIs)	X	To be reported at any time during the study from D01 to D31 (+14 days) after study vaccination		
End of Active Phase participation record‡	X			X

AESI: Adverse Events of Special Interest; CRF: case report form; SAE: Serious Adverse Events
* Should a participant receive oral or injectable antibiotic therapy within 3 days prior to each blood draw, the Investigator will postpone that blood draw until it has been 3 days since the participant last received oral or injectable antibiotic therapy. Postponement is still to be within the timeframe for blood draw (30 to 44 days after vaccination at D01). If postponement will

result in the sample collection falling outside of the appropriate timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

† Blood sample at D01 will be drawn before administration of the vaccine

‡In case of participant discontinuation at a visit, the entire visit will be completed. Active Phase is from Visit 1 to Visit 2 completion.

§ The Investigator or an authorized designee will remind the parents, guardians, or legally acceptable representatives to bring back the diary card (DC) at the next visit and will answer any questions. If D09 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the participant experienced any SAEs (including AESIs) not yet reported and will remind the participant's parent/guardian to continue using the diary card, to bring the diary card to the study center at the next visit and confirm the date and time of the next visit.

**The Investigator or an authorized designee will interview the parents, guardians, or legally acceptable representatives to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

2 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 2.1.

Table 2.1: Objectives and endpoints

Objectives	Endpoints
Immunogenicity	**Immunogenicity**
1) To describe the immune response to a booster dose of MenQuadfi® as measured by the serum bactericidal assay using human complement (hSBA) in toddlers aged 12-23 months, who had been primed with at least 1 dose of another MCV4 vaccine during infancy	1) hSBA antibody titers ≥ 1:8 (seroprotection) against meningococcal serogroups A, C, W and Y at D31 (+14 days) after booster vaccination with MenQuadfi®
2) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy	2) At Day (D)01 (baseline) before vaccination and at D31 [+14 days] after the administration of a booster dose of MenQuadfi® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by hSBA: • Antibody titers against meningococcal serogroups A, C, W, and Y • Antibody titers ≥ 1:4 and ≥ 1:8 • ≥ 4-fold rise from pre-vaccination to post-vaccination
3) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with 2 doses of another MCV4 vaccine during infancy	• Vaccine seroresponse, defined as follows: • For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16 • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer
4) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with 1 dose of another MCV4 vaccine during infancy	At Day (D)01 (baseline) before vaccination and at D31 [+14 days] after the administration of a booster dose of MenQuadfi® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by rSBA: • Antibody titers against meningococcal serogroups A, C, W, and Y • Antibody titers ≥ 1:8 and ≥ 1:128 • ≥ 4-fold rise from pre-vaccination to post-vaccination
5) To describe the antibody responses to tetanus toxoid before and 1 month after a booster dose of MenQuadfi® in toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy	• Vaccine seroresponse defined as follows: • For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32 • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer 3) Same endpoints as described for endpoint #2 4) Same endpoints as described for endpoint #2 5) Antibody concentrations against tetanus toxoid at D01 (baseline) and at D31 (+14 days) after the administration of a booster dose of MenQuadfi®

Safety	**Safety**
• To describe the safety profile of a booster dose of MenQuadfi® administered to toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy	• Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination. • Presence of solicited (pre-listed in the participant's diary card [DC] and case report form [CRF]) injection site reactions up to 7 days after vaccination. • Presence of solicited systemic reactions (pre-listed in the participant's DC and CRF) up to 7 days after vaccination. • Presence of unsolicited AEs up to 30 days after vaccination. • Presence of serious adverse events (SAEs) [including AESIs], throughout the trial from Visit 1 to 30 days after study vaccination. Depending on the items, the endpoints recorded or derived could include: • Nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to the vaccine, whether the AE led to early termination from the study, outcome, and seriousness criterion

3 Statistical Considerations

3.1 Statistical Hypotheses

No hypotheses will be tested. The analyses will be descriptive.

3.2 Sample Size Determination

There are no statistically powered hypotheses in this study thus no formal sample size computation. All analyses will be descriptive.

The sample size was set to approximatively 180 participants (minimum of 30 evaluable participants from the low - enrolling of the 2 priming vaccines) to have at least 150 evaluable participants assuming a drop-out rate of approximatively 15%.

In terms of immunogenicity for any of the 4 serogroups, considering a sample size of 150 evaluable participants, the expected precision of the 95% CI using the Exact binomial method will be as follow:

Seroprotection rates (titer >= 1:8)	**Precision***
85%	13.77
90%	11.62
95%	8.96
100%	2.88

*Difference between the upper and lower bounds of the 95%CI

In terms of safety, the planned sample size will allow for identification of common AEs. One hundred and fifty evaluable participants will allow with 95% probability, the detection of an AE occurring with a frequency of 2% or more, using the rule of threes.

3.3 Populations for Analyses

The following populations are defined:

Participant Analysis Set	Description
Safety Analysis Set (SafAS)	Participants who have received the study vaccine. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of SafAS.

	Participants who received the study vaccine and had a valid post-vaccination serology result. Participants will be analyzed according to the intervention they received.
Per-protocol analysis set (PPAS)	Subset of FAS. Participants presenting with at least 1 of the following relevant protocol deviations will be excluded from the PPAS: • Participant did not meet all protocol-specified inclusion criteria/exclusion criteria • Participant did not receive the study vaccine • Preparation and/or administration of vaccine was not done as per-protocol • Participant did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn (Blood sampling 2 (BL0002) / Visit 2: Visit 1+ 30 day (+14 days)) • Participant's post-dose serology sample did not produce a valid test result (i.e., results for all meningococcal antigens are missing) • Participant had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database • Participant received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine

3.4 Statistical Analyses

3.4.1 General Considerations

Immunogenicity parameters will be analyzed in specified analysis sets (PPAS and FAS) in the overall population, as well as by primed vaccine groups.
Safety analysis will be performed on the SafAS.

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 or later.

For descriptive purposes, the following statistics will be presented:

Table 3.1: Descriptive statistics produced

Disposition and follow-up description	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Baseline characteristics	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs for main endpoints) of participants. Unsolicited: Number and percentage (95% CIs for main endpoints) of participants and number of events.
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cutoff)**	Number and percentage (95% CIs for main endpoints) of participants
	Continuous data (titer / data†)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1), i.e., using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

3.4.2 Immunogenicity Endpoints

Descriptive statistics will be provided for the hSBA and rSBA antibody titers against meningococcal serogroups (A, C, W, and Y) and for antibody concentrations against tetanus toxoid contained in MenQuadfi® as a carrier protein.

All immunogenicity analyses will be performed on the PPAS and FAS.

In general, categorical variables will be summarized and presented by frequency counts, proportion percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the Exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

For immunogenicity data, assuming that log10 transformation of the titers / concentrations follows a normal distribution, first, the mean and 95% CIs will be calculated on log10 (titers / concentrations) using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, to compute GMTs / GMCs and their 95% CIs.

Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups and the antibody concentrations against tetanus toxoid contained in MenQuadfi®.

In summary, descriptive analyses on A, C, Y, and W serogroups on D01 and D31 after vaccination with MenACYW conjugate vaccine will include but not be limited to:

- hSBA and rSBA seroprotection rate (titer ≥ 1:8) and 95% CI
- hSBA and rSBA GMTs and 95% CI
- hSBA and rSBA titer distribution and RCDC
- Percentage of participants with hSBA titer ≥ 1:4 and 95% CI
- Percentage of participants with rSBA titer ≥ 1:128 and 95% CI
- Percentage of participants with hSBA and rSBA titer ≥4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of participants with hSBA and rSBA vaccine seroresponse rate and 95% CI
  hSBA vaccine seroresponse for serogroups A, C, Y, and W defined as:
  - For a participant with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16
  - For a participant with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

  rSBA vaccine seroresponse defined as:
  - a post-vaccination rSBA titer ≥ 1:32 for participants with pre-vaccination rSBA titer < 1:8, or
  - a post-vaccination titer ≥ 4 times the pre-vaccination titer for participants with pre-vaccination rSBA titer ≥ 1:8

In addition, descriptive analyses on anti-tetanus antibody concentrations will include but not be limited to:

- GMCs and 95% CI
- The percentage of participants with antibody concentrations to tetanus toxoid ≥ 0.01 international units (IU)/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL and 95% CI

3.4.3 Safety Endpoints

Safety analyses will be performed on the SafAS and presented overall. The main parameters for the safety endpoints will be described by 95% CIs using the Exact binomial method (Clopper-Pearson method).
The safety analysis that will be presented by priming vaccines status for the following safety summary tables :

- Safety overview after MenACYW conjugate vaccine dose received at V01,
- Summary of unsolicited AEs within 30 days after MenACYW conjugate vaccine dose received at V01
- Overview of SAEs.

3.4.4 Handling of Missing Data and Outliers

Generally, no replacement will be done for Safety Missing Data and Outliers. For immunogenicity, no imputation of missing values and no search for outliers will be performed.

3.4.4.1 Safety

3.4.5.1.1 Immediate

For unsolicited systemic AEs, a missing response to the “Immediate” field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

3.4.5.1.2 Causal Relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.5.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.5.1.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset

will be included in analyses within or not within the defined time window (according to the Section 4.2.1.2.4), according to the last vaccination (computed according to the Section 4.2.1.2.3),. If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

3.4.5.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.4.2 Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described in Section 4.2.3.1.

3.5 Interim Analysis

An interim report may be generated with hSBA analysis of all immunogenicity endpoints and safety endpoints depending on the timelines regarding the availability of the rSBA data. Final report will be generated with the analyses of rSBA immunogenicity endpoints.

This study will not include an early safety data review. No additional analyses are planned to be performed prior to the formal completion of the study.

3.6 Data Monitoring Committee (DMC)

Not applicable.

4 Complementary Information on Assessment Methods

Study assessments and procedures are detailed in Section 8 of the protocol. This section focusses on complementary/additional information not detailed in the protocol.

4.1 Complementary Information for Endpoints Assessment Methods

Not applicable.

4.2 Complementary Information on Derived Endpoints: Calculation Methods

4.2.1 Safety

4.2.1.1 Solicited Reactions

4.2.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as “No” and with all daily records missing (Unknown) then all daily intensities will be derived as None.

2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, “NM”) is Grade 3.

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

Table 4.1: Solicited injection site reactions: terminology, definitions, and intensity scales – Infants and toddlers aged ≤ 23 months

CRF term (MedDRA lowest level term [LLT])	Injection site tenderness	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition	Pain when the injection site is touched or injected limb mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	**Grade 1:** CRF and DC: Minor reaction when injection site is touched **Grade 2:** CRF and DC: Cries or protests when injection site is touched **Grade 3**: CRF: Cries when injected limb is mobilized, or the movement of the injected limb is reduced DC: Cries when injected limb is moved or the movement of the injected limb is reduced	**Grade 1:** > 0 to < 25 mm **Grade 2:** ≥ 25 to < 50 mm **Grade 3:** ≥ 50 mm	**Grade 1:** > 0 to < 25 mm **Grade 2:** ≥ 25 to < 50 mm **Grade 3:** ≥ 50 mm

* For tenderness, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grade 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 4.2: Solicited systemic reactions: terminology, definitions, and intensity scales – Infants and toddlers aged ≤ 23 months

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
						fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	**Grade 1:** ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F	**Grade 1:** CRF and DC: 1 episode per 24 hours	**Grade 1:** CRF and DC: < 1 hour	**Grade 1:** CRF and DC: Sleepier than usual or less interested in surroundings	**Grade 1:** CRF and DC: Eating less than normal	**Grade 1:** CRF and DC: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	**Grade 2:** CRF and DC: 2–5 episodes per 24 hours	**Grade 2:** CRF and DC: 1–3 hours	**Grade 2:** CRF and DC: Not interested in surroundings or did not wake up for a feed / meal	**Grade 2:** CRF and DC: Missed 1 or 2 feeds / meals completely	**Grade 2:** CRF and DC: Requiring increased attention
	Grade 3: > 39.5°C **or** > 103.1°F	**Grade 3** CRF: ≥ 6 episodes per 24 hours or requiring parenteral hydration DC: at least 6 episodes per 24 hours or requiring intravenous hydration (fluids administered in the arm or leg)	**Grade 3:** CRF and DC: > 3 hours	**Grade 3:** CRF and DC: Sleeping most of the time or difficult to wake up	**Grade 3:** CRF and DC: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	**Grade 3:** CRF: Inconsolable DC: Inconsolable (cannot be comforted)

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

4.2.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.1.1.3 Presence

Presence is derived from the maximum overall intensity over the time period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing or Unknown: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

The time period is displayed as D1-D4, D5-D8, D9 and later.

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

Time of onset period is displayed as, D1-D4, D5-D8.

4.2.1.1.5 Number of Days of Presence During the Solicited Period

Number of days of presence over the solicited period (D1-D8) considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

4.2.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

(End date - last vaccination date) + (number of days of presence within the solicited period) - length of the solicited period + 1

If the end date is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: If the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1.
- Not ongoing: If the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in safety tables).

4.2.1.2 Unsolicited AEs

4.2.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

Grade 0 events are not included in safety analysis but are included in separate listings.

4.2.1.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Intensity for the other unsolicited AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.2.1.2.3 Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the CRF and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE
- If an unsolicited AE has a partially missing start date and there is clear evidence about the last vaccination from the partially missing start date, then the start date is used to determine the last vaccination before the unsolicited. Situations may happen as:

    - If the start date of AE has missing Day and non-missing Month and Year

- If the "Month/Year of vaccination (i) date" < "Month/Year of AE start date" < "Month/Year of vaccination (i+1) date", then it is clear that the last vaccination before this unsolicited AE is the vaccination i.
- If the "Month/Year of vaccination (i) date" < "Month/Year of AE start date" and there is no injection (i+1), then it is clear that the last vaccination before this unsolicited AE is the vaccination i.

- If the start date of AE has missing Day and Month and non-missing Year:

- If the "Year of vaccination (i) date" < "Year of AE start date" < "Year of vaccination (i+1) date", then it is clear that the last vaccination before this unsolicited AE is the vaccination i.
- If the "Year of vaccination (i) date" < "Year of AE start date" and there is no injection (i+1), then it is clear that the last vaccination before this unsolicited AE is the vaccination i.

- If the start date is missing or partially missing (with no clear evidence about the last vaccination), or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE.

4.2.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination as described in Section 4.2.1.2.3:

Time of Onset = start date of the unsolicited AE - date of last vaccination before the unsolicited AE + 1.

The time of onset is considered as missing only if one or both dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 30 days" after each vaccination, which corresponds to AEs with a time of onset between 1 and 31 days.

Unsolicited AE that occurred before vaccination (negative time of onset) will not be included in analysis but will be listed separately.

- For unsolicited AE with missing day, month and year, the unsolicited AE will be classified as "Within 30 days"
- For unsolicited AE with partially missing start date, the partial available information will be used to determine if this AE is classified "Within 30 days" or "Not within 30 days". An AE will be categorized as "Not within 30 days" only if there is clear evidence from

the partially missing start date that this AE happens before the first vaccination or after the last vaccination + 30 days. In all other situations, this AE is considered as "Within 30 days". Situations may happen as:

- If the start date of AE has missing Day and non-missing Month and Year

  - If the "Month/Year of AE start date" < "Month/Year of first vaccination date", then it is clear that this unsolicited AE happened before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.
  - Else if the "Month/Year of last vaccination date" <= "Month/Year of AE start date" <= "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
  - Else if the "Month/Year of AE start date" > "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days".

- If the start date of AE has missing Day and Month and non-missing Year:

  - If the "Year of AE start date" < "Year of first vaccination date", then it is clear that this unsolicited AE happens before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.
  - Else if the "Year of last vaccination date" <= "Year of AE start date" <= "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
  - Else if the "Year of AE start date" > "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days".

A few examples of missing time of onset with start date of AE partially missing:

First injection date	Last injection date	Start date of the AE	Injection date + 30	Will be analyzed "Within 30 days" ?
16Oct2023	16Oct2023	Missing	N/A	Y
16Oct2023	16Oct2023	Sep2023	N/A	N
16Oct2023	16Oct2023	Oct2023	15Nov2023	Y
16Oct2023	16Oct2023	Nov2023	15Nov2023	Y
16Oct2023	16Oct2023	Dec2023	15Nov2023	N
05Jan2023	05Jan2023	2022	N/A	N
16Oct2023	16Oct2023	2023	15Nov2023	Y
08Dec2023	08Dec2023	2024	07Jan2024	Y
16Oct2023	16Oct2023	2024	15Nov2023	N

Time of onset period is displayed as D1-D4, D5-D8, D9-D15, D16 or later, and Missing.

4.2.1.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE:

Duration = End date of unsolicited AE – start date of unsolicited AE + 1.

The duration is considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

4.2.1.2.6 Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF. SAEs will be analyzed throughout the study using the following periods:

- Within 7 days
- Within 30 days
- During the study (i.e., all SAEs occurred during the study)

4.2.1.2.7 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF.

AESIs will be analyzed throughout the study using the following periods:

- Within 7 days
- Within 30 days
- During the study (i.e., all AESIs occurred during the study)

4.2.2 Other Safety Endpoints

4.2.2.1 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.2.2.2 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.2.2.3 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.2.2.4 Causal Relationship

This information will be summarized as collected in the field "Relationship to study vaccine". Missing causal relationship will be handled as described in Section 3.4.5.1.2 . Relationship to study procedure is only presented in the listing.

4.2.2.5 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.
In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Study" form question "What was the participant's status?" has "Adverse Event" checked.

- Safety overview table: A participant who has either on the "Completion at End of Study" form, question "What was the participant's status?" has "Adverse Event" checked or lists a solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

- System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

4.2.3 Immunogenicity

4.2.3.1 Computed Values for Analysis

In order to appropriately manage extreme values (< LLOQ and ≥ ULOQ) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample (BL) drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

4.2.3.2 Seroprotection

For each meningococcal serogroups A, C, W, and Y measured by hSBA:

- If the computed value is ≥ 1:8, then the derived seroprotection indicator will be “Yes” for that test, otherwise seroprotection will be "No". Note: If the computed value is missing, seroprotection will be missing.

4.2.3.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows. Generally, for extreme values, this algorithm minimizes the numerator and maximizes the denominator.

- If the baseline computed value is < LLOQ and the post-baseline computed value is < LLOQ, then the fold-rise is 1
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is ≥ LLOQ, then the fold-rise is post-baseline computed value / baseline computed value
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is < LLOQ, then the fold-rise is (LLOQ/2) / baseline computed value
- If the baseline computed value is < LLOQ and the post-baseline computed value is ≥ LLOQ, then the fold-rise is post-baseline computed value /LLOQ

Note: If baseline or post-baseline is missing, then fold-rise is missing.

4.2.3.4 hSBA Vaccine Seroresponse

For each meningococcal serogroups A, C, W, and Y measured by hSBA:

- The derived seroresponse indicator for hSBA will be “Yes”:
  - if the pre-vaccination at baseline titer is < 1:8 and the post-vaccination titer ≥ 1:16
  - or if the pre-vaccination at baseline titer is ≥ 1:8 and the post-vaccination is a ≥ 4-fold increase than the pre-vaccination titer.

4.2.3.5 rSBA Vaccine Seroresponse

For each meningococcal serogroups A, C, W, and Y measured by rSBA:

- The derived seroresponse indicator for rSBA will be "Yes":
  - if the pre-vaccination at baseline titer is < 1:8 and the post-vaccination titer ≥ 1:32
  - or if the pre-vaccination at baseline titer is ≥ 1:8 and the post-vaccination is a ≥ 4-fold increase than the baseline titer at post-vaccination

4.2.4 Efficacy

Not applicable.

4.2.5 Derived Other Variables

4.2.5.1 Age for Demographics

The participant's date of birth (DOB) and date of enrollment are collected as part of the demographic information. The participant's age is then automatically calculated and populated in the electronic Case Report Form (CRF) based on the DOB provided. Specifically, the field labeled 'Age' is auto-filled, and the age is calculated in months, with the result presented as an integer.

4.2.5.2 Temperature

The temperature of a participant in the study is computed as the maximum between the evening temperature and the additional observed daily temperature.

4.2.5.3 Duration of a Participant in the Trial

The duration of a participant in the study is computed as follows:

Maximum (date of last visit, date of termination) – (date of Visit 1 of that participant) +1.

4.2.5.4 Duration of the Study

The durations are computed in days as follows: Latest period date - Earliest period date + 1.

5 Changes in the Conduct of the Trial or Planned Analyses

Immunogenicity results by number of doses received in the priming schedule will not be described because we only have participants who had 2 priming doses of meningococcal quadrivalent vaccination.

The sample size was set to approximatively 180 participants (minimum of 30 evaluable participants from the low - enrolling of the 2 priming vaccines) to have at least 150 evaluable participants assuming a drop-out rate of approximatively 15%, however the recruitment had to be stopped before reaching 180 subjects in total (and minimum of 30 evaluable participants enrolling of the 2 priming vaccines), due to the low recruitment rate. Mitigation plan was set up and the recruitment period was extended but finally when no more improvement was possible it was decided in agreement with the principal investigator to stop the recruitment as the analysis are descriptive.

COVID FORM was not applied to the study as due to administrative issue study was pushed further and started only after COVID was no more of a Pandemic issue.

As per diary card structure both Evening temperature and Additional temperature are collected. The highest temperature will be used for statistical analysis.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sampling
CI	confidence interval
CRF	case report form
D	day
DC	diary card
DMC	Data Monitoring Committee
DOB	date of birth
DOV	date of visit
FAS	full analysis set
GMC	geometric mean concentration
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
IM	intramuscular
LLOQ	lower limit of quantification
LLT	lowest level term
MCV4	quadrivalent meningococcal conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
PPAS	per-protocol analysis set
RCDC	reverse cumulative distribution curve
rSBA	serum bactericidal antibody assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SoA	schedule of activities
TC	telephone call
TT	tetanus toxoid
ULOQ	upper limit of quantification

7 References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.