NCT: NCT06228586

SAP Core Body

Title: A Phase III, open-label, single-center study to describe the immunogenicity and safety of a single dose of MenACYW Conjugate Vaccine in participants aged 12 months and older in Vietnam

Study Code: MEQ00074

Study Phase: Phase III

SAP Core Body Version: 1.0

SAP Core Body Date: 21 January 2025

Protocol Version Number: 1.0

The SAP Core Body should be used in conjunction of the study protocol and the SAP TLF (if applicable).

Version History

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

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1 Overall Design

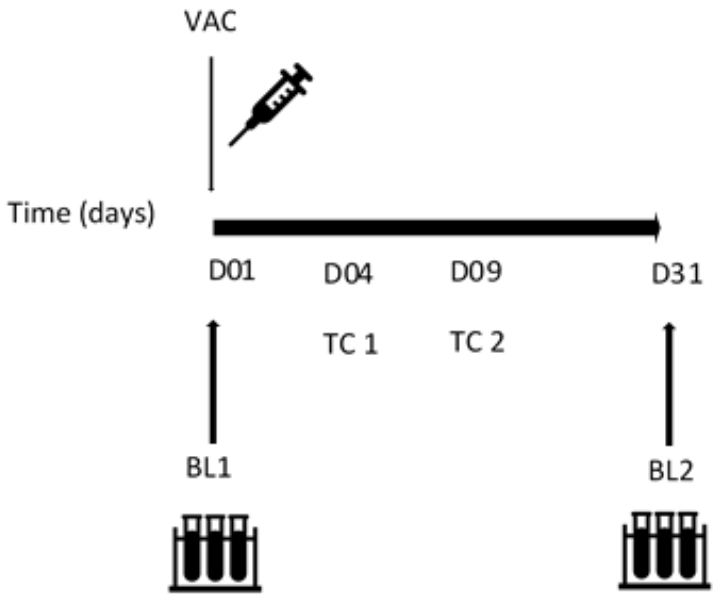
The design of the table is summarized in Table 1.1.

Table 1.1: Overall design

Type of design	Single group, single-center
Phase	III
Control method	Uncontrolled
Study population	Meningococcal vaccination naïve, healthy toddlers, children, adolescents, adults and older adults aged 12 months and above
Level and method of blinding	Open-label
Study intervention assignment method	Not applicable
Number of participants	A total of 446 participants are expected to be enrolled with the aim to obtain a total of 400 evaluable participants: • 223 participants will be 12-23 months of age • 223 participants will be 24 months of age and above. To ensure all sub-groups are represented, a minimum of 20 participants will be enrolled from each of the sub-groups mentioned below: • Children 2 to 9 years of age • Adolescents 10 to 17 years of age • Adults 18 to 55 years of age • Older adults 56 years and above
Intervention groups	All eligible participants will receive a single intramuscular injection of MenACYW conjugate vaccine
Total duration of study participation	The duration of each participant's participation will be approximately 30 to 44 days
Country	Vietnam
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

The study design of MEQ00074 study is presented in Figure 1.1.

Figure 1.1: Graphical study design



BL: blood sample; TC: telephone call; VAC: vaccination

The schedule of activities are given in Table 1.2

Table 1.2: Schedule of activities

Phase III Study, 2 Visits, 2 Telephone calls, 1 Vaccination, 2 Blood Samples, 30 to 44 Days' Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	TC1	TC2	Visit 2
Study timelines (days)		D01	D04 Visit 1 + 3 days	D09 Visit 1 + 8 days	D31 Visit 1 + 30 days
Time windows (days)		-	+2 days	+2 days	+14 days
Visit procedures:					
Informed consent/assent*	X	X			
Inclusion/exclusion criteria	X	X			
Collection of demographic data	X	X			
Urine pregnancy test (if applicable)		X			
Collection of significant medical history	X	X			
Physical examination (including pre-vaccination temperature)**		X			
Review of temporary contraindications for blood sampling †	X				X
Blood sampling (BL) ‡ [3 mL]	X	BL0001			BL0002
Vaccination	X	X			
Immediate surveillance (30 min)	X	X			
Information on DC provided		X			
Telephone call (TC) §	X		X	X	
Collection of solicited injection site and systemic reactions**	X	Day 1 to Day 8			
Collection of unsolicited AEs	X	Visit 1 to Visit 2			
DC reviewed and information collected					X
Collection of reportable concomitant medications	X	X			X
Collection of SAEs, including AESIs ††	X	To be reported at any time during the study period			
Collection of pregnancies	X	To be reported at any time during the study period			
End of study participation record ‡‡	X				X

Abbreviations: AE: adverse event; AESI: adverse events of special interest; BL: blood sampling; CRF: case report form; DC: diary card; SAE: serious adverse event; TC: telephone call

* Assent required for participants aged 12 to 15 years.

**Physical examination should be performed as per standard of care. If a routine examination had been performed within the last week by the Investigator, a sub-Investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area. Temperature needs to be measured before vaccination and daily during the 7 days after vaccination and recorded in the DC.

†Should a participant receive oral or injectable antibiotic therapy within 3 days prior to any 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 must still be within the timeframe for blood draw. If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be appropriately documented that the sample was taken less than 3 days after stopping antibiotic treatment.

‡Blood sample at Visit 1 to be drawn before administration of the vaccine.

§The first telephone call will be made 3 days to 5 days after the vaccination. The second telephone call will be made 8 days to 10 days after the vaccination. If Day 04 (+ 2 days) and Day 09 (+2 days) fall 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 SAE (including any AESI) not yet reported, and will remind the participant/participant's parent/legally acceptable representative to continue using the DC, bring the DC to the study center at the next visit, and confirm the date and time of the next visit.

** Solicited injection site and systemic reactions will be recorded from the day of vaccination through 7 days after vaccination.

††AESI will be collected throughout the study as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causal relationship

‡‡ In case of participant discontinuation at a visit, the entire visit will be completed.

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	
• To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a single dose of MenACYW conjugate vaccine	Antibody titers against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) will be assessed before and 30 days after vaccination with a single dose of MenACYW conjugate vaccine.
Safety	
• To describe the safety profile of a single dose of MenACYW conjugate vaccine	The safety profile will be evaluated within 30 days (+14 days) after vaccination. The following endpoints will be used for the evaluation of safety: • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Presence of solicited (prelisted in the participant's diary card [DC] and case report form [CRF]) injection site and systemic reactions starting any time from the day of vaccination through 7 days after vaccination • Presence of unsolicited (recorded in a DC) non-serious AEs up to 30 days after vaccination; unsolicited non-serious AEs occurring after D31 will be presented in a specific listing • Presence of serious adverse events (SAEs) (including adverse events of special interest [AESIs]) throughout the study, ie from D01 (vaccination) to the last study day D31; SAEs occurring after D31 are also to be reported if they are considered related to vaccination with the investigational medicinal product (IMP) 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 statistical hypotheses will be tested. Descriptive statistics will be presented.

3.2 Sample Size Determination

There are no statistically powered hypotheses in this study. No formal sample size calculations were performed.

A total of 446 participants will be enrolled in the study, 223 participants will be enrolled in age category 12 months to 23 months, 223 participants will be enrolled in age category 24 months and above. An estimated 10% non-adherence rate from enrollment will result in approximately 400 evaluable participants in total, and 200 evaluable participants in each age category (12 months – 23 months, ≥ 24 months).

The overall evaluable study cohort (N=400) will provide a probability of approximately 95% of observing any AE (at least 1 occurrence) with a true incidence of 0.75%.

For participants aged 12 to 23 months, 200 participants will provide a probability of approximately 95% of observing any AE (at least 1 occurrence) with a true incidence of 1.5%.

For participants aged 24 months and above, 200 participants will provide a probability of approximately 95% of observing any AE (at least 1 occurrence) with a true incidence of 1.5%.

3.3 Populations for Analyses

The following populations are defined for immunogenicity and safety analyses:

Analysis Set	Description
Safety analysis set (SafAS)	Participants who have received the study vaccine and have any safety data available.
Full analysis set (FAS)	Participants who received the study vaccine and had a valid post-vaccination serology result.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: • Participants did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria

	• Participant did not receive vaccine • Preparation and / or administration of vaccine was not done as per-protocol • Participants did not provide the post-dose serology sample at Visit 2 in the proper time window or a post-dose serology sample was not drawn • Participants received a category 2 or 3 protocol-prohibited therapy / medication / vaccine • Participants had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database. In addition to the reasons listed above, participants will also be excluded from the PPAS if their Visit 2 serology sample did not produce a valid test result.

3.4 Statistical Analyses

3.4.1 General Considerations

Safety and immunogenicity parameters will be analyzed in specified analysis sets in the overall population, as well as by age categories (12 months – 23 months, ≥ 24 months).

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 Endpoint

No statistical hypotheses will be tested. Descriptive statistics will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y by using hSBA before and 30 days after a single dose of meningococcal conjugate vaccine.
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All immunogenicity analyses will be performed on the PPAS and the FAS.

In general, categorical variables will be summarized and presented by frequency counts, 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 log10-normally distributed.

Descriptive analyses of antibody responses to A, C, W, and Y serogroups using hSBA will include but not be limited to:

- hSBA seroprotection rate (titer ≥ 1:8) and 95% CI
- GMTs and 95% CI.
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- Percentage of participants with titers ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of participants with hSBA titers ≥ 1:4, and 95% CI
- Percentage of participants with hSBA vaccine seroresponse, and 95% CI
  Note: hSBA vaccine seroresponse for serogroups A, C, W, and Y is 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

3.4.3 Safety Endpoint

No statistical hypotheses will be tested.

Safety results will be described for participants in the study. The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method).

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.

All safety analyses will be performed on the SafAS.

3.4.4 Handling of Missing Data and Outliers

3.4.4.1 Safety

Generally, no replacement will be done for Safety Missing Data and Outliers.

3.4.4.1.1 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.

3.4.4.1.2 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.

3.4.4.1.3 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.

3.4.4.1.4 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.

3.4.4.1.5 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

No 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

Subgroup Analysis

Additional subgroup analyses by age categories (12 Months-23 Months, Children 2 to 9 years of age, Adolescents 10 to 17 years of age, Adults 18 to 55 years of age and older adults 56 years and above) for immunogenicity and safety parameters for all populations analysis sets.

The following parameters will be assessed before and 30 days after the vaccination:

- hSBA seroprotection rate (titer ⩾ 1:8) and 95% CI
- GMTs with 95% CI
- Percentage of participants with titer ≥ 1:4 and 95% CI
- Percentage of participants with hSBA vaccine seroresponse and 95% CI
- Percentage of participants with titers ⩾ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI

The safety overview will be also described by age subgroups.

4.1.1 Definition of enrolled participants

Enrolled study participants are study participants that had their eligibility evaluation and passed screening.

For this study only enrolled participants will be analyzed.

4.1.2 Sensitivity Analysis due to Blood Sample Issues

If more than 10% participant had blood samples not suitable for use. Then additional immunogenicity sensitivity analyses will be performed for subjects with blood samples handled incorrectly during collection, processing, storage or shipment, and may have potential impact on the analysis results (eg, blood samples stored out of temperature after a power outage) based on the PPASs. The outputs will be provided in Appendix 15 of the CSR.

The following immunogenicity parameters will be assessed:

- hSBA seroprotection rate (titer ≥ 1:8) and 95% CI
- GMTs with 95% CI
- Percentage of participants with titer ≥ 1:4 and 95% CI
- Percentage of participants with hSBA vaccine seroresponse and 95% CI
- Percentage of participants with titers ⩾ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI

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 intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

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: Minor reaction when injection site is touched Grade 2: 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 Grade 3 **(diary card)**: 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

MedDRA: Medical Dictionary for Regulatory Activities
* 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 injection site reactions: terminology, definitions, and intensity scales – Children aged 2 through 11 years

CRF term (MedDRA lowest level term [LLT])	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is 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*	**CRF:** Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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

MedDRA: Medical Dictionary for Regulatory Activities
* For pain, 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 Grades 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 4.3 : Solicited injection site reactions: terminology, definitions, and intensity scales – Adolescents and adults aged ≥ 12 years

CRF term (MedDRA lowest level term [LLT])	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is 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*	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

	Grade 3: Significant; prevents usual activities		

MedDRA: Medical Dictionary for Regulatory Activities
* For pain, 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 Grades 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 4.4 : 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	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 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 Grade 2: > 38.5°C to ≤ 39.5°C	Grade 1: 1 episode per 24 hours Grade 2: 2–5 episodes per 24 hours	Grade 1: < 1 hour Grade 2: 1–3 hours	Grade 1: Sleepier than usual or less interested in surroundings Grade 2: Not interested in surroundings or did not wake up for a feed / meal	Grade 1: Eating less than normal Grade 2: Missed 1 or 2 feeds / meals completely	Grade 1: Easily consolable Grade 2: Requiring increased attention

	Grade 3: > 39.5°C	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	Grade 3: Inconsolable

MedDRA: Medical Dictionary for Regulatory Activities
* 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.

Table 4.5 : Solicited systemic reactions: terminology, definitions, and intensity scales – Children aged 2 through 11 years, adolescents or adults aged ≥ 12 years

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only

		minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
	Grade 2: ≥ 38.5°C to ≤ 38.9°C Grade 3: ≥ 39.0°C	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities

MedDRA: Medical Dictionary for Regulatory Activities
* 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 computed 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. 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 period 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 inSection 4.2.1.1.1and 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. *Note the intensity could be considered None (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).*

- 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 the 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. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but < 25 mm in adults).

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 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.2.2.2 Action Taken

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

4.2.2.3 Seriousness

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

4.2.2.4 Outcome

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

4.2.2.5 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 3.4.4.1.2.. Relationship to study procedure is only presented in the listing.

4.2.2.6 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 (undetectable responses < the lower limit of quantitation [LLOQ] and ≥ the upper limit of quantitation [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample 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

hSBA vaccine seroprotection is defined as: hSBA titers ≥ 1:8.

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 A/C/Y/W Vaccine Seroresponse

hSBA Vaccine seroresponse for serogroups A, C, Y, and W is defined as either:

- Post-vaccination hSBA titers ≥ 1:16, if pre-vaccination hSBA titers < 1:8 or
- At least a 4-fold increase in hSBA titers from pre- to post-vaccination, if pre-vaccination hSBA titers ≥ 1:8.

4.2.4 Efficacy

Not applicable.

4.2.5 Derived Other Variables

4.2.5.1 Age for Demographics

For participants from 12 months to 23 months, the age of a participant in the study was collected in months at the time of inclusion.
For participants from 24 months and above, the age of a participant in the study was collected in years at the time of inclusion.

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 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

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

For this study, screening failure information were not supposed to be collected according to the protocol. But inadvertently, this information was collected by the site, and it was integrated into several raw databases. This was due to fast recruitment in short period of time. The screen failures will be excluded from the main analysis. Their information will be presented in separate listing. The screen failures list was retrieved by the programming team and later was validated by the investigator. Sanofi team identified this issues and retraining was insured. But, the majority of recruitment was completed by then.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
BL	Blood sample
CI	Confidence interval
COVID19	Coronavirus disease 2019
CRF	Case report form
DC	Diary card
FAS	Full analysis set
GMT	Geometric mean titer
hSBA	Serum bactericidal assay using human complement
IMP	Investigational medicinal product
ITT	Intent-to-treat
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per protocol
PPAS	Per-protocol analysis set
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse event
SafAS	Safety analysis set
SAP	Statistical analysis plan
TC	Telephone call

7 References

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