SANOFI PASTEUR

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Potential Pilgrims Aged 56 Years and Older

A Phase III, open-label, study to describe the immunogenicity and safety of MenACYW conjugate vaccine in potential pilgrims ≥ 56 years of age in Turkey and Lebanon

Statistical Analysis Plan (SAP) - Core Body Part

NCT Number: NCT03869866

Trial Code:	MEQ00063
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur 14 Espace Henry Vallée 69007, Lyon France
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular (IM)
Indication For This Study:	Potential pilgrims aged 56 years and older
Version and Date of the SAP core body part:	Version 2.0, 30November2022

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List of Abbreviations

AE	adverse event
AESI(s)	Adverse event(s) of special interest
BL	blood sample
CI	confidence interval
CRB	case report book
CRF	electronic case report form
D	day
ECL	electrochemiluminescence
FAS	full analysis set
GM	geometric mean
GMC	geometric mean concentrations
GMT	geometric mean titers
GMTR	geometric mean titer ratio
hSBA	serum bactericidal assay using human complement
IMD	invasive meningococcal disease
IU	international unit
KSA	Kingdom of Saudi Arabia
LLOQ	lower limit of quantitation
MD	missing data
PPAS	per-protocol analysis set
PT	preferred term
RCDC	reverse cumulative distribution curve
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SOC	system organ class (primary)
ULOQ	upper limit of quantitation

1 Introduction

This trial will describe the immunogenicity and safety profiles of a single dose of the quadrivalent Meningococcal Polysaccharide (Serogroups A, C, Y and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in adult pilgrims 56 years of age and older.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis* (*N. meningitidis*), a Gram-negative diplococcus found exclusively in humans. At least 12 distinct meningococcal serogroups have been classified based on the immunochemistry of the capsular polysaccharides (PS). The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. Meningococcal disease occurs worldwide in both endemic and epidemic forms with seasonal variation.

Every year more than 2 million people from all over the world undertake the Hajj, the annual pilgrimage to Mecca. The Hajj is an epidemiological phenomenon. Because of crowds, high humidity, and air pollution, the carriage rate of *N. meningitidis* can be as high as 80% which eventually may cause epidemics.

Epidemics during the Hajj have been known for decades. After the first documented international outbreak caused by serogroup A, vaccination was mandated for pilgrims to enter the Kingdom of Saudi Arabia (KSA). Starting in 2002, following serogroup-W outbreaks in 2000 and 2001, the requirement for vaccination with bivalent AC vaccine was switched to quadrivalent (ACYW) polysaccharide vaccine (29). Visitors arriving for the purpose of Umrah or pilgrimage (Hajj) are required to submit a certificate of vaccination with the tetravalent (ACYW) vaccine against meningitis, proving the vaccine was administered no less than 10 days before arrival in KSA. Both polysaccharide and conjugate vaccines are valid options.

The goal for MenACYW conjugate vaccine is to provide broad protection against invasive meningococcal disease (IMD) caused by serogroups A, C, W, and Y in all age groups including children as young as 6 weeks of age, adolescents, and adults, including those 56 years of age and older.

MenACYW conjugate vaccine was found to be well tolerated and no unanticipated or new significant safety concerns have been identified in the clinical trials completed to date or in the ongoing studies.

The KSA has a long history of instituting preventative measures against meningococcal disease. KSA is at risk of outbreaks of meningococcal disease due to its geographic location, demography, and especially because it hosts the annual Hajj and Umrah mass gatherings.

The mandatory meningococcal vaccination policy for pilgrims has possibly been the major factor in preventing outbreaks during the pilgrimages and has also probably been important in reducing the carriage and transmission of *Neisseria meningitidis* in KSA and beyond. The preventative measures for Hajj and Umrah favor the conjugate vaccine for its extra benefits over the polysaccharide vaccines. The Hajj in 2012 and 2013 attracted more than 5 million pilgrims from 184 countries. Most of these pilgrims are part of the elderly population.

2 Trial Objectives

Immunogenicity

- To describe the antibody response to meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using baby rabbit complement (rSBA) before and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine
- To describe the antibody response to meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) before and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine
- To describe the antibody responses against tetanus toxoid at baseline and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine

Safety

- To describe the safety profile of a single dose of MenACYW conjugate vaccine

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase III, open-label, study to describe the immunogenicity and safety of MenACYW conjugate vaccine in potential pilgrims ≥ 56 years of age in Turkey and Lebanon.

Approximately 330 healthy adults were to be enrolled in the study to receive a single dose of MenACYW conjugate vaccine.

All subjects will provide pre-vaccination blood samples for immunogenicity assessment at baseline (Visit 1) and at Day (D) 30 (+14-day window) post-vaccination (Visit 2).

Safety data were to be collected as follow: Immediate unsolicited systemic adverse events (AEs) were to be collected within 30 minutes after vaccination. Solicited AE information was to be collected for 7 days after vaccination, unsolicited AE information was to be collected from Visit 1 to Visit 2, and SAE information (including adverse events of special interest [AESIs]) was to be collected from Visit 1 through Visit 2.

A certificate of vaccination was to be given to each subject after vaccination. The individual subject immunogenicity results were to be made available to the study Investigator once they are available. The Investigator was to communicate the study results to the individual subjects. Any subsequent clinical intervention, if needed, were to be the responsibility of the Investigator based on his/ her clinical judgement and outside of the scope of this protocol. If the antibody titers against meningococcal serogroups A, C, W, and Y measured by rSBA did not reach the protective titer of ≥ 1:8 for one of the serogroups included in the vaccine, the Investigator was to advise whether, in light of a potential pilgrimage for Hajj or Umrah in the following 5 years, vaccination with a licensed quadrivalent meningococcal conjugate vaccine was necessary.

3.2 Trial Plan

A schedule of assessments and study vaccinations is provided in Table 3.1.

Vaccination

All subjects will receive a single dose of MenACYW conjugate vaccine at Visit 1 (D0).

Blood Sampling

All subjects will provide a pre-vaccination blood sample at Visit 1 and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination at Visit 1).

Collection of safety data

- All subjects will be followed for safety from Visit 1 (D0) to Visit 2.
- All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time were to be recorded as immediate unsolicited systemic AEs in the case report book (CRB).
- The subject will record information in a diary card about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to Visit 2.
- SAEs (including AESIs) will be recorded throughout the duration of the trial. The subject will record information in a diary card about SAEs from D0 to Visit 2.
- The subject will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- Staff will also contact subjects by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card up to Visit 2 and to bring it back to Visit 2.
- The completed diary card will be reviewed with the subject at Visit 2.

Table 3.1: Study procedures

Phase III Trial, 2 Visits, 1 Vaccination, 2 Blood Samples, 1 Telephone Call,
30 to 44 Days duration per Subject

Visit/Contact	Visit 1	Telephone Call	Visit 2
Trial timelines (days)	D0	D08	D30
Time windows (days)	NA	+2 days	+14 days
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Urine pregnancy test (if applicable)	X		
Medical history	X		
Physical examination*	X		
Allocation of subject number	X		
Review of temporary contraindications for blood sampling †			X
Blood sampling (BL), 10 mL‡§	BL0001		BL0002
Vaccination	X		
Immediate surveillance (30 min)	X		
Diary card provided	X		
Telephone call		X§	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited non-serious AEs	D0 to Visit 2		
Diary card reviewed and collected			X
Reporting of SAEs (including AESIs)**	To be reported throughout the study period		
Collection of reportable concomitant medications	X		X
Trial termination record			X

* Temperature needs to be measured and recorded in source documents.

† Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator was to postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at Visit 1). 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 documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

‡ A pre-vaccination blood sample was to be collected from all subjects at D0.

§ This call is made 8 to10 days after the vaccinations on D0. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff was to find out whether the subject experienced any SAE not yet reported, and was to remind the subject to continue using the diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2.

** AESIs were to be collected throughout the trial 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 causality.

4 Endpoints and Assessment Methods

4.1 Immunogenicity

The endpoints for the evaluation of immunogenicity are:

- Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y measured by rSBA assessed at 30 days (+14 days) after vaccination with a single dose of MenACYW conjugate vaccine
- Antibody titers against meningococcal serogroups A, C, W, and Y measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine
- Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine
- Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested for anti-tetanus antibodies by electrochemiluminescence (ECL).

The following endpoints will be assessed:

- Antibody concentrations to tetanus toxoid at both pre- and post-vaccination time points, geometric mean concentrations (GMCs)
- The proportion of subjects achieving seroprotective levels ≥ 0.01 International Units (IU) /milliliters (mL) and ≥ 0.1 IU/mL of antibody concentrations to tetanus toxoid at both pre- and post-vaccination time points

See section 9.1.1 of the protocol for the description of the immunogenicity assessment methods used.

4.2 Safety

The following endpoints will be used for all subjects for the evaluation of safety:

- Unsolicited systemic AEs reported in the 30 minutes after the vaccination, including occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, relationship to the product administered, and whether the event caused termination from the study.
- Solicited (prelisted in the subject's diary card and CRB) injection site and systemic reactions starting any time from Day 0 (day of vaccination) through Day 7 after the vaccination, including occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction caused termination from the study.
- Unsolicited AEs occurring up to Visit 2, including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered (for systemic AEs only), and whether the event caused termination from the study.

- SAEs (including AESIs) reported throughout the trial, including occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to the product administered, whether the event caused termination from the study, outcome.

See Section 9.2 of the protocol for more details.

Table 4.1 and Table 4.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 4.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
MedDRA preferred term (PT)	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Erythema	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*	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.	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

* For the subjective reaction of pain, subjects will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

Table 4.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia
MedDRA PT	Pyrexia	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥ 38.0°C (≥ 100.4°F)	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, or ≥ 100.4°F to ≤ 101.1°F	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 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 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: ≥ 38.5°C to ≤ 38.9°C, or ≥ 101.2°F to ≤ 102.0°F	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 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 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.

CRB term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia
	Grade 3: ≥ 39.0°C or ≥ 102.1°F	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.	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.	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.

* For all reactions but fever, subjects will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, 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.

4.3 Derived Endpoints: Calculation Methods

4.3.1 Safety

4.3.1.1 Solicited Reactions

4.3.1.1.1 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.

4.3.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.3.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.3.1.1.3 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

Subjects 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 D0-D3, D4-D7, D8 and later.

4.3.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.3.1.1.1. 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.

4.3.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.3.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

4.3.1.1.6 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 occurrence 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 occurrence 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 occurrence will be considered as Missing.

4.3.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.3.1.1.1 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 the safety tables).

4.3.1.2 Unsolicited AEs

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

4.3.1.2.1 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.

4.3.1.2.2 Intensity

Intensity will be defined 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 Table 4.1 and Table 4.2 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.

4.3.1.2.3 Last Vaccination

Since there is only one vaccination in this study, last vaccination before an unsolicited AE is the study vaccination at V01.

4.3.1.2.4 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 4.3.1.2.3:

> Time of Onset = start date of the unsolicited AE – date of last vaccination before the unsolicited AE

The time of onset is considered as missing only if one or both of the 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 0 and 30 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the Section 4.3.1.2.3), so will be included in these tables.

Time of onset period is displayed as D0-D3, D4-D7, D8-D14, D15 or later, and Missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis but will be listed separately.

4.3.1.2.5 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.

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

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

4.3.1.5 Other Safety Endpoints

4.3.1.5.1 Pregnancy

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

4.3.1.5.2 Action Taken

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

4.3.1.5.3 Seriousness

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

4.3.1.5.4 Outcome

This information will be summarized as collected for Unsolicited non-serious AEs and SAEs. No derivation or imputation will be done.

4.3.1.5.5 Causal relationship

This information will be summarized as collected in the field "Relationship to Investigational Product". Missing causal relationship will be handled as described in Section 5.3.1.2. Relationship to study procedure is only presented in the listing.

4.3.1.5.6 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 subject 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.

4.3.2 Immunogenicity

4.3.2.1 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

4.3.2.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows:

- Calculate the fold-rise of values as the ratio of post-baseline computed value divided by baseline computed value

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

4.3.2.3 hSBA Vaccine Seroresponse

The derived vaccine seroresponse indicator for hSBA will be "Yes" if:

- hSBA titer is < 1:8 at baseline with a post-baseline hSBA titer ≥ 1:16
- or hSBA titer is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-baseline

4.3.2.4 rSBA Vaccine Seroresponse

The derived vaccine seroresponse indicator for rSBA will be "Yes" if

- rSBA titer is < 1:8 at baseline with a post-baseline rSBA titer ≥ 1:32
- or rSBA titer is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-baseline

4.3.2.5 Efficacy

Not applicable

4.3.3 Derived Other Variables

4.3.3.1 Age for Demographics

The age of a subject in the study was the calendar age in years at the time of inclusion.

4.3.3.2 Duration of a Subject in the Trial

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

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

4.3.3.3 Duration of the Study

The duration of the study is computed as follows:

Maximum of all subjects (date of last visit, date of termination) – Minimum of all subjects (date of Visit 1) + 1.

5 Statistical Methods and Determination of Sample Size

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

The results of the statistical analysis will be available in the final clinical study report. For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (vaccine seroresponse, ≥ 4-fold rise, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / concentration)	Log_{10}: Mean and standard deviation. Anti-Log_{10} (work on Log10 distribution, and anti-Log_{10} applied): Geometric mean (GM), 95% CI of the GM. 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)). For immunogenicity results, assuming that Log_{10} transformation of the titers follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log_{10} (titers) 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 GMs and their 95% CI.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Objectives

5.1.1.1 Hypotheses

No hypotheses will be tested. Descriptive statistics will be presented.

5.1.1.2 Statistical Methods

Immunogenicity

Immunogenicity results will be described. The reverse cumulative distribution curves (RCDCs) and distribution tables will also be produced for the antibody titers against meningococcal serogroups A, C, Y and W. The parameters will be described with 95% confidence interval (CI).

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 (1).

For geometric mean titers (GMTs) or geometric mean concentrations (GMCs) 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

In summary, descriptive analyses on A, C, Y, and W serogroups will include but not be limited to:

Parameters	rSBA analysis	hSBA analysis
GMC at D0 and D30	X	X
GMT ratio (GMTR) (D30/D0)	X	X
Titer distribution at D0 and D30	X	X
Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination (D0) to postvaccination (D30)	X	X
Percentage of subjects with vaccine seroresponse based on D0 and D30 titers	X	X
Percentage of subjects with titer ≥ 1:4 at D0 and D30		X
Percentage of subjects with titer ≥ 1:8 at D0 and D30	X	X
Percentage of subjects with titer ≥ 1:128 at D0 and D30	X	

Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested for anti-tetanus antibodies by ECL. The following parameters will be assessed:

- Geometric mean concentrations (GMCs) at D0 and D30
- Percentage of subjects achieving seroprotective levels ≥ 0.01 IU/mL and ≥ 0.1 IU/mL of antibody concentrations to tetanus toxoid at D0 and D30

Safety

Safety results will be descriptive. The 95% CIs of point estimates will be calculated using the exact binomial distribution (Clopper-Pearson method) for percentages

5.1.2 Complementary analysis

Complementary outputs by country will be provided based on main immunogenicity and safety parameters and disposition tables.

The impact of COVID-19 pandemic situation on study conduct will be summarized through impact on visit procedures, study completion and major/critical protocol deviations due to COVID-19.

The subjects impacted by COVID-19 pandemic situation will be defined as the subjects with at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19. If more than 10% of subjects are impacted as per this definition, baseline and demographics characteristics, and the main immunogenicity and safety endpoints will also be summarized in the subsets of subjects impacted/ non-impacted subjects to assess the potential impact of COVID-19 situation on study outcome.

5.2 Analysis Sets

Three analysis sets will be used: the Full Analysis Set (FAS), the Per-Protocol Analysis Set (PPAS), and the Safety Analysis Set (SafAS).

5.2.1 Full Analysis Set

The FAS is defined as the subset of subjects who received at least one dose of the study vaccine and had a valid post-vaccination serology result.

5.2.2 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Preparation and/or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample at Visit 2 in the proper time window (Visit 1 + 30 to 44 days) or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy/medication/vaccine (Category 2 or Category 3)
- Subject's serology sample at Visit 2 did not produce a valid test result (i.e., results for all antigens are missing).
- Subject had another protocol deviation that affected the subject's immune response, as determined by the clinical team before locking the database

This list may not be exhaustive. The above protocol deviations leading to exclusion from the PPAS may be completed if necessary following data review process. The PPAS definition will be finalized before the database lock.

5.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received at least 1 dose of the study vaccine and have any safety data available.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis and listed separately.

5.2.4 Populations Used in Analyses

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

All safety analyses will be performed on the SafAS.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

No replacement will be done. In all subject listings, partial and missing data will be clearly indicated as missing.

5.3.1.1 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.

5.3.1.2 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.

5.3.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.3.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.3.1.4 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 according to the last vaccination (computed according to the Section 4.3.1.2.3). 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.

5.3.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

Missing data will not be imputed. No test or search for outliers will be performed.

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

The sample size was arbitrarily chosen to be 280 evaluable subjects. Assuming an attrition rate of approximately 15%, a total of 330 subjects will be included in the study. In order to balance the age of subjects at enrollment, between 50 and 130 enrolled subjects should be ≥ 75 years of age.

Assuming seroprotection rates of 95% or more (rSBA), a sample size of 280 evaluable subjects per group will ensure a 95% CI with a precision of no more than 5.4% (using the exact binomial method).

Assuming seroprotection rates of 75% or more (hSBA), a sample size of 280 evaluable subjects per group will ensure a 95% CI with a precision of no more than 10.5% (using the exact binomial method).

In terms of safety, the planned sample size will allow for identification of common AEs. A sample size of 280 evaluable subjects allows, with 95% probability, for the detection of an AE occurring with a frequency of 1.1% or more, using the rule of threes.

5.6 Data Review for Statistical Purposes

A review of the data has been anticipated through the data review process led by data management before database lock. This review of the data included a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

5.7.1 Analysis

It is anticipated to have several months of delay to obtain the rSBA results after the LVLS.

Therefore the statistical analysis will be done in two steps as follow:

- A first statistical analysis of the safety and immunogenicity data (except rSBA data) will be done following a database lock with provision. All data included at this stage will be final and won't be modified in later analyses.

- A final statistical analysis will be performed including rSBA data after final database lock.

5.7.2 Sample size

A total of 330 subjects were initially planned to be enrolled. Due to coronavirus disease 2019 (COVID-19) pandemic, the recruitment period was extended. A total of 290 subjects were actually enrolled in the study.

5.7.3 Reportable medications

Categories of reportable medications were updated and defined as:
• Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids [therapy duration less than 2 weeks], and other immune-modulators)
Category 1 medication do not define the Per-Protocol Analysis Set (PPAS).
Note: Topical steroids (inhaled, optic, ophthalmic, nasal, etc.) should not be captured or reported.
Category 1 medications will be reported in the CRF from the day of each vaccination to the end of the solicited and unsolicited follow-up period after each vaccination.
• Category 2: medications impacting or that may have an impact on the immune response and used to define the PPAS; for example:
- Flu vaccines administered within 14 days pre or post each trial vaccination, including the day of the study vaccination visit
- Any vaccine (including COVID-19 vaccine) other than study vaccines (vaccines not described in the Protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study vaccination visit
- Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
- Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) used in the past 3 months preceding the study vaccination and up to the last blood draw, anti-cancer chemotherapy, antiproliferative drugs such as deoxyribonucleic acid (DNA) synthesis inhibitors, or radiation therapy: used in the 6 months preceding the first study vaccination, and up to the last blood draw

Category 2 medications will be reported in the CRF during the study period and up to the last blood draw.
• Category 3: systemic (oral or injectable) antibiotics received within 72 hours preceding each visit for blood draw related to IMP assessment (meningococcal vaccines) and used to define the PPAS, as they may interfere with bioassays used for antibody testing when taken before a blood draw
Category 3 medications will be reported in the CRF for the period of 3 days (72 hours) before each blood draw.
Note: Topical antibiotics (Inhaled, optic, ophthalmic, nasal, etc.) should not be captured or reported.
The information reported in the CRF for each reported medication will be limited to:
- Trade name
- Rationale for the origin of prescription: Whether it was a prophylactic[a] medication?

[a] Participant's parents/legally acceptable representatives will be required to document all medications received in the diary cards. The sites will focus on only recording the medications belonging to the 3 categories in the other source documents.

Prophylactic medications will be recorded in the Action Taken section of the AE collection tables.

- Medication category (1, 2, or 3)
- Start and stop dates

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site,
they should be recorded as a Category 1 medication in this specific instance.
If the participant has received medications other than those listed in Categories 1, 2, and 3, the detailed information will be collected in the source documents only.
Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication received belongs to one of the pre-listed categories. Medications will not be coded.

6 References List

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