SANOFI PASTEUR

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered in Healthy Children 2 to 9 Years of Age

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to a licensed quadrivalent meningococcal conjugate vaccine in healthy children 2 to 9 years of age in the United States

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET35
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
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:	MenACYW conjugate vaccine as a single dose for children 2 to 9 years
Version and Date of the SAP core body part:	Version 2.0, 28 Feb 2018 This SAP version 2.0 is the first amendment to the initial trial SAP version 1.0, dated 11 OCT 2016.

NCT Number: NCT03077438

History of SAP Versions

Table 1: Previous versions of the SAP

Version*	Date	Comments
1.0	11 October 2016	Original SAP; first version used in the study
2.0	28 February 2018	Amendment 1

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List of Abbreviations

AE	adverse event
[redacted]	[redacted]
AR	adverse reaction
BL	blood sample
CFU	colony - forming unit
CI	confidence interval
CRF	electronic case report form
D	day
EDC	electronic data capture
FAS	Full Analysis Set
GBS	Guillain-Barré syndrome
GM	geometric mean
GMT	geometric mean titer
GMTR	geometric mean titer ratio
hSBA	serum bactericidal assay using human complement
ICF	informed consent form
ICH	International Conference on Harmonisation
IMD	invasive meningococcal disease
ITP	idiopathic thrombocytopenic purpura
LLOQ	lower limit of quantitation
LLT	lowest level term
MA	memory aid
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter(s)
N.	*Neisseria*
PPAS	Per-Protocol Analysis Set
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
UAR	unexpected adverse reaction
ULOQ	upper limit of quantitation

1 Introduction

This trial (MET35) will evaluate the immunogenicity and safety 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 children 2 to 9 years of age. The purpose of the MET35 trial is to demonstrate that the immunogenicity and safety profiles of the MenACYW conjugate vaccine are comparable with those of MENVEO® in this age group.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis (N. meningitidis)*, a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (2) (3) (4).

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. In Europe, the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 19 year old group. In the US, the incidence rate of IMD was 0.14 per 100,000 in all ages; 0.83 per 100,000 in infants less than 1 year; 0.62 per 100,000 in toddlers 1 year of age; 0.27 per 100,000 in children 2 to 4 years of age; and 0.02 per 100,000 in children 5 to 17 years of age in 2013. The age specific incidence rate per 100,000 was 0.08 in adults 50 to 64 years of age, 0.03 in adults 65 to 74 years of age, 0.14 in adults 75 to 84 years of age, and 0.43 in adults 85 years of age and older in 2013(5).

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

The MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 to 55 years of age; and MET32, a Phase I/II study in toddlers.

The formulation has been evaluated in over 1639 subjects (infants, toddlers, adolescents, and adults > 55 years of age) in completed studies MET39, MET44, MET50, and MET54. MenACYW conjugate vaccine is also being evaluated in an ongoing Phase III study (MET56 in adolescents and adults).

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 MET56 study.

The purpose of MET35 is to demonstrate that the immunogenicity profile of a single dose of the MenACYW conjugate vaccine in children 2 to 9 years of age is comparable with MENVEO®, a US licensed quadrivalent diphtheria CRM_{197} protein conjugate meningococcal vaccine, and describe the safety profiles of both vaccines.

2 Trial Objectives

2.1 Primary Objective

To demonstrate the non-inferiority of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine compared to that observed following the administration of a single dose of MENVEO® in children aged 2 to 9 years

The endpoints for the primary objective are presented in Section 4.1.1.1.

2.2 Secondary Objectives

1) To compare the serum bactericidal assays using human complement (hSBA) antibody geometric mean titers (GMTs) of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine to those observed following the administration of MENVEO® in children aged 2 to 9 years of age
2) To evaluate the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine and those observed following the administration of MENVEO® in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively
3) To evaluate the hSBA vaccine seroresponse to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) post-vaccination in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively

The endpoints for the secondary objectives are presented in Section 4.2.1.1.

2.3 Observational Objectives

Immunogenicity

1) To describe the antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or MENVEO®
2) To describe the antibody titers against meningococcal serogroups A, C, Y, and W measured by (serum bactericidal assays using baby rabbit complement) rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or MENVEO® in a subset of subjects

Safety

To describe the safety profile of MenACYW conjugate vaccine and that of the licensed MENVEO®

The endpoints for the observational objectives are presented in Section 4.3.1.1 and Section 4.3.2.2, for immunogenicity and safety, respectively.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to the MENVEO® in healthy children 2 to 9 years of age in the United States.

Healthy, meningococcal-vaccine naïve children aged 2 to 9 years will be randomized in a 1:1 ratio as follows:

- Group 1: MenACYW conjugate vaccine: N = 500
  - Group 1a: 250 children 2 to 5 years of age[a]
  - Group 1b: 250 children 6 to 9 years of age[b]
- Group 2: MENVEO®: N = 500
  - Group 2a: 250 children 2 to 5 years of age[a]
  - Group 2b: 250 children 6 to 9 years of age[b]

All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days after vaccination.

Solicited adverse event (AE) information will be collected for 7 days after vaccination; unsolicited AE information will be collected from Visit 1 (Day [D] 0) to Visit 2 (D30 [+14 days]) and serious adverse event (SAE) information [redacted] will be collected throughout the study period from D0 through D180 (+14 days) after vaccination.

Medically-attended adverse events (MAAEs) will be collected throughout the study from Visit 1 through Visit 2 (as part of the collection of unsolicited AE information) and from Visit 2 through D180 (+14 days) (as MAAEs).

3.2 Trial Plan

A schedule of assessments and study vaccinations is provided in the Table of Study Procedures.

Vaccination

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

Blood Sampling

All subjects will provide a pre-vaccination blood sample at D0 and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination at Visit 1).

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[a] "2 to 5 years of age" means from the day of the 2nd birthday to the day before the 6th birthday

[b] "6 to 9 years of age" means from the day of the 6th birthday to the day before the 10th birthday

Antibodies to meningococcal serogroups A, C, Y, and W antigens will be measured by hSBA for all subjects, and by rSBA for a subset of subjects.

Table 3.1: Testing strategy for *N meningitidis* serogroups A, C, Y, and W

	ACYW serogroups tested by hSBA* (all subjects)	ACYW serogroups tested by rSBA† (subset)
Group 1		
Group 1a (2 to 5 years old)	250	100
Group 1b (6 to 9 years old)	250	100
Group 2		
Group 2a (2 to 5 years old)	250	100
Group 2b (6 to 9 years old)	250	100

* hSBA: serum bactericidal assay using human complement
† rSBA: serum bactericidal assay using baby rabbit complement

Collection of Safety Data

- All subjects will be observed for 30 minutes after vaccination and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the electronic case report form (CRF) (see Section 4.3.2.3.1).
- The subject's parent / guardian 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 will be reported throughout the duration of the trial.
- The subject's parent / guardian will record information only about possible SAEs and MAAEs in a memory aid (MA) from Visit 2 until the 6-month (+14 days) telephone call.
- In addition, the subject's parent / guardian will be asked to notify the site immediately about potential SAEs at any time during the trial.
- Staff will contact the subject's parent / guardian 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 at Visit 2.
- The completed diary card will be reviewed with the subject's parent / guardian at Visit 2.
- Staff will contact the subject's parent / guardian by telephone at 6 months (+14 days) post-vaccination to review the MA and identify the occurrence of any MAAEs as well as SAEs that may not have been reported.

Table 3.2: Study procedures

Phase III Trial, 2 Visits, 1 Vaccination, 2 Telephone Calls, 2 Blood Samples, 180 Days Duration per Subject

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2
Trial timelines (days)	D0	D08	D30	D180
Time windows (days)	--	+2 days	+14 days	+14 days
Informed consent form/assent form (if applicable)	X			
Inclusion/exclusion criteria	X			
Collection of demographic data	X			
Urine pregnancy test (if applicable)	X			
Medical history	X			
Physical examination*	X			
Review of temporary contraindications for blood sampling†			X	
Randomization/allocation of subject number	X			
Blood sampling (BL), 5 mL‡	BL1		BL2	
Vaccination§	X			
Immediate surveillance (30 minutes)	X			
Diary card provided	X			
Telephone call		X**		X††
Recording of solicited injection site & systemic reactions	D0 to D07			
Recording of unsolicited AEs	D0 to Visit 2			
Recording of MAAEs‡‡				After Visit 2 to TC2
Reporting of SAEs [redacted]	To be reported throughout the study period			
Diary card reviewed and collected			X	
Collection of reportable concomitant medications	X		X	
Memory aid (MA) provided***			X	
Termination of active phase of trial			X	
Completion of 6-month follow-up				X

*Temperature needs to be measured by axillary, oral, or rectal route (axillary is the preferred route) 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 will 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 D0). 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.

‡Blood sample at Visit 1 will be drawn before administration of vaccine

§Subjects will receive a single dose of MenACYW conjugate vaccine or a single dose of MENVEO®.

**This call is made 8 to 10 days after the vaccination at Visit 1. 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 will find out whether the subject experienced any SAE not yet reported, and will remind the subject's parent/guardian 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.

††Staff will contact the subject's parent/guardian by telephone at 6 months (180 days +14 days) after vaccination at Visit 1 to identify the occurrence of any MAAEs as well as SAEs not yet reported.

‡‡MAAEs that occur between Visit 1 and Visit 2 will be recorded as unsolicited AEs.

§§ [redacted]

***The MA is used for the recording of SAEs and MAAEs. The site staff will make a telephone call to the parent/guardian to obtain the information 180 days (+14 days) after the vaccination at Visit 1. Since the timeframe between Visit 1 and Visit 2 (inclusive) will be captured in the diary card, the MA will be used to collect SAE and MAAE data from Visit 2 to TC2.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Immunogenicity

4.1.1.1 Immunogenicity Endpoint

The primary endpoint for the evaluation of immunogenicity is:

- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assays using human complement (hSBA) assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination.

4.1.1.2 Immunogenicity Assessment Method

[redacted]

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Immunogenicity

4.2.1.1 Immunogenicity Endpoints

The secondary endpoints for immunogenicity are:

- GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or MENVEO®
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or MENVEO®

4.2.1.2 Immunogenicity Assessment Method

The immunogenicity hSBA assessment method for the secondary endpoints is the same as that presented in Section 4.1.1.2.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Immunogenicity

4.3.1.1 Immunogenicity Endpoints

The observational endpoints for immunogenicity are:

1) Antibody titers against meningococcal serogroups A, C,Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine or MENVEO®
2) Antibody titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days after vaccination with MenACYW conjugate vaccine or MENVEO® in a subset of subjects

4.3.1.2 Immunogenicity Assessment Methods

[redacted]

This method will be performed on a subset of BL1 and BL2 samples corresponding to 100 subjects in each of the following groups, Group 1a, Group 1b, Group 2a, and Group 2b, respectively (400 subjects total).

In the event of insufficient serum sample volume, the conduct of the hSBA is of higher priority than the rSBA.

4.3.2 Safety

4.3.2.1 Safety Definitions

The following definitions are taken from the International Conference on Harmonisation (ICH) E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore an AE may be:

- A new illness
- The worsening of a concomitant illness
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

Surgical procedures are not AEs; they are the action taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the trial period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious* which is based on patient / event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability / incapacity[c]
- Is a congenital anomaly / birth defect
- Is an important medical event[d]

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

Unexpected Adverse Reaction (UAR):

An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the CRF**.** The assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of:

- Symptom and
- Onset post-vaccination

Examples of solicited reactions include injection site pain between D0 and D07 post-vaccination or headache between D0 and D07.

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[a] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or out-patient treatment with no hospitalization.

[c] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[d] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, GBS, new onset diabetes, or autoimmune disease.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and / or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D07 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D07 is a solicited reaction, whereas headache starting on D08 post-vaccination is an unsolicited AE.

An unsolicited non-serious AE is an unsolicited AE excluding SAEs.

Injection Site Reaction:

An injection site reaction[a] is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions.

Systemic AE:

Systemic AEs are all AEs that are not injection site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination site, e.g., erythema that is localized but that is not at the injection site.

[redacted]

Medically-Attended Adverse Event (MAAE)

An MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject or subject's parent/guardian to seek unplanned medical advice at a physician's office or Emergency Department. This definition excludes pre-planned medical office visits for routine pediatric check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. Physician contact made over the phone or by email will be considered a physician office visit for the purpose of MAAE collection. The outcome of the physician contact (whether it results in a prescription or not) will not be considered as a basis for reporting the event as an MAAE and all contacts should be reported. Sufficient data should be collected for the event to allow an assessment of the causality and diagnosis, if possible.

[a] All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

4.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and electronic case report form [CRF]) injection site reactions occurring up to 7 days after vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to Visit 2 after vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs [redacted] throughout the trial.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness, relationship to vaccination, and outcome for MAAEs from Visit 2 to the 6-month follow-up contact. MAAEs will be collected as unsolicited AEs up to Visit 2.

4.3.2.3 Safety Assessment Methods

At Visit 2, the Investigator or a delegate will ask the subject's parent / guardian about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRF according to the instructions provided by the Sponsor.

4.3.2.3.1 Immediate Post-vaccination Surveillance Period

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination surveillance should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the CRF, as follows:

- Any unsolicited systemic AE occurring during the first 30 minutes post-vaccination will be recorded on the CRF as immediate unsolicited systemic AE.
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded and analyzed as starting on the day of vaccination.

- Any SAE occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in the protocol.

4.3.2.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 07 After Vaccination)

After vaccination, subjects' parents / guardians will be provided with a safety diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (i.e., D0 to D07) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event, if any (e.g., medication)

The action taken by the parent or guardian to treat any solicited reactions will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

4: Hospitalization (inpatient)

Subjects' parents / guardians will be contacted by telephone 8 days after vaccination to remind them to record all safety information in the diary card.

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, study staff will continue calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

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

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

CRF term (MedDRA lowest level term [LLT])	Injection site pain*	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition		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: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform 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

*For the subjective reaction of pain, subjects or parents / guardians 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

CRF term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥ 100.4°F (≥ 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: ≥ 100.4°F to ≤ 101.1°F **or** ≥ 38.0°C to ≤ 38.4°C Grade 2: ≥ 101.2°F to ≤ 102.0°F **or** ≥ 38.5°C to ≤ 38.9°C Grade 3: ≥ 102.1°F **or** ≥ 39.0°C	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

*For all reactions but fever, subjects or parents / guardians 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.

Important notes for the accurate assessment of temperature:

Parents / guardians are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRF. The preferred route for this trial is axillary. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic thermometers must not be used.

4.3.2.3.3 Unsolicited Non-serious Adverse Events From Day 0 to Day 30 After Vaccination

In addition to recording solicited reactions, parents / guardians will be instructed to record any other medical events that may occur during the 30-day period after vaccination. Space will be provided in the diary card for this purpose.

For each unsolicited non-serious AE, the following information is to be recorded:

- Start and stop dates[a]
- Intensity of the event:
  - For measurable unsolicited non-serious AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 4.1 and Table 4.2)
  - Other unsolicited non-serious AEs will be classified according to the following intensity scale:
    - Grade 1: No interference with activity
    - Grade 2: Some interference with activity
    - Grade 3: Significant; prevents daily activity
- Action taken for each AE, if any (e.g., medication)

The action taken by the parent or guardian to treat any unsolicited AEs will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

[a] The stop date of all related AEs will be actively solicited. For other events, the investigator will provide the stop date when it becomes available. AEs for which no stop date was obtained during the course of the trial will be considered as ongoing at the end of the trial.

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

- Whether the AE led to discontinuation
- Whether the AE was related to vaccination (for unsolicited systemic AEs)

4.3.2.3.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from inclusion until 180 days after the last vaccination. The collection of SAEs begins at the time of first dose and ends 180 days (+14 days) post last dose.

Any SAE occurring at any time during the trial will be reported by the Investigator through the electronic data capture (EDC) system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE is to be reported, either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). The Investigator will assess the causal relationship between the SAE and the investigational product as either "Not related" or "Related", as described in Section 4.3.2.3.7.

In case a subject experiences convulsion / seizure episode associated or not with fever, this event will be considered an SAE.

See protocol for further details on SAE reporting.

[redacted]

4.3.2.3.6 Medically-Attended Adverse Events

MAAE information will be collected throughout the study. MAAEs that occur from Visit 1 (D0) to Visit 2 (D30[+14days]) will be recorded as unsolicited AEs on the diary card as part of all

unsolicited AEs collected for this post-vaccination period. MAAEs that occur from Visit 2 (D30 [+14 days]) to D180 (+14 days) will be recorded as such in the memory aid. An MAAE that occurs within the study period but meets the definition of an SAE should be reported only on the SAE Reporting Form, but not on the MAAE page of the CRF. The Investigator will assess the causal relationship between the MAAE and the investigational or study product as either "Not related" or "Related", as described in Section 4.3.2.3.7.

4.3.2.3.7 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and vaccination as either not related or related, based on the following definitions[a]:

0: Not related – The AE is clearly / most probably caused by other etiologies such as subject's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable)

1: Related – There is a "reasonable possibility" that the AE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all injection site AEs (solicited and unsolicited) and all solicited systemic reactions are considered to be related to vaccination and referred to as reactions, and therefore do not require the Investigator's opinion on relatedness.

AEs likely to be related to the product, whether serious or not, that persist at the end of the trial will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 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.

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

1) Solicited reactions (except Fever) with an investigator presence recorded as "No" and with all daily records missing then all daily intensities will be derived as None.

[a] ICH Guidelines, Clinical Safety Data Management E2A

2) For a temperature partially missing after decimal point, the data will be analyzed replacing "MD" (missing data) by zero. For example, a "39.MD" daily temperature will be considered as "39.0°C" at the time of analysis.

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

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

4.4.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

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

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. 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.

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. 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.

4.4.1.1.6 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 stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

- (stop date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the stop date is missing or incomplete (contains missing data [MD]), the overall number of days of occurrence will be considered as Missing.

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 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.

If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

4.4.1.2 Unsolicited Non-serious AEs

4.4.1.2.1 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 should be included in the listing "Unsolicited non-serious AEs not included in the safety analysis."

4.4.1.2.2 Intensity

Intensity for unsolicited non-serious AEs will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited non-serious 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 as the intensity scales defined in Section 4.4.1.1.1 for that measurable injection site or systemic reaction.

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

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

4.4.1.2.3 Last Vaccination

Last vaccination before any unsolicited non-serious AE is the study vaccination at V01.

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

- start date of the unsolicited non-serious AE – date of previous vaccination

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

The unsolicited non-serious AEs will be analyzed "Within 30 days", 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 vaccination indicated by the visit number, so will be included in these tables.

Note: Unsolicited non-serious AEs 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.

4.4.1.2.5 Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

- stop date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if one or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

4.4.1.3 SAEs

4.4.1.3.1 Last Vaccination

Last vaccination before any SAE is the study vaccination at V01.

4.4.1.3.2 Time of Onset

Time of onset will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.4.

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

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

An SAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: SAEs that occurred before vaccination (negative time of onset) will not be included in analysis, but will be listed separately.

4.4.1.3.3 Duration

Duration will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.5.

4.4.1.4 Medically-Attended Adverse Events

MAAEs that occur from Visit 1 (D0) to Visit 2 (D30[+14days]) will be recorded as unsolicited AEs on the diary card as part of all unsolicited AEs collected. Unsolicited AEs that have action taken categories 2 (health care provider contact) or 3 (Health care contact + Medication) will be summarized and presented as MAAEs between D0 visit and D30 visit.

MAAEs that occur from Visit 2 (D30 [+14 days]) to D180 (+14 days) will be recorded as such in the memory aid. An MAAE that occurs within the study period but meets the definition of an SAE should be reported only on the SAE Reporting Form, but not on the MAAE page of the CRF. Calculation methods are the same as unsolicited non-serious AEs as described in Section 4.4.1.2.

4.4.1.5 Other Safety Endpoints

4.4.1.5.1 Action Taken

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

4.4.1.5.2 Seriousness

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

4.4.1.5.3 Outcome

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

4.4.1.5.4 Causality

This information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.5.5 AEs Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination “Serious Adverse Event” or “Other adverse event” is checked.

- Safety overview table: A subject who has either the reason for early termination "Serious Adverse Event" or "Other adverse event" checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked on the termination form, that is at least Grade 1 and is within the time period indicated
- System organ class/preferred term (SOC/PT) table: An event (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked that is at least Grade 1 and is within the time period indicated

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

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

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

4.4.2.2 Seroprotection

Not applicable

4.4.2.3 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.

4.4.2.4 A, C, Y, W Seroresponse

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

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

rSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

- Post-vaccination rSBA titers ≥ 1:32, if pre-vaccination rSBA titers < 1:8 or
- At least a 4-fold increase in rSBA titers from pre- to post-vaccination, if pre-vaccination rSBA titers ≥ 1:8.

4.4.3 Efficacy

Not applicable

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

Age in years: (Date of vaccination - Date of birth +1) / 365.25

4.4.4.2 Subject Duration

The duration of a subject in the study is computed as follows: Maximum (date of last visit, date of term form) – (date of Visit 1) +1.

The duration of a subject in the study including follow-up is computed as follows: Maximum (date of last visit, date of term form, last date of follow-up contact) – (date of Visit 1) +1.

4.4.4.3 Duration of the Study

The duration of the study (until last visit) is computed as follows: Maximum of all subjects (date of last visit, date of termination form) – minimum for all subjects (date of Visit 1) +1.

The duration of the study (including follow-up) is computed as follows: Maximum of all subjects (date of last visit, date of termination form, date of last follow-up contact) – minimum for all subjects (date of visit V01) +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 (CSR).

For descriptive purposes, the following statistics in Table 5.1 will be presented. The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (6)). For immunogenicity results, assuming that Log_{10} transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log_{10} (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.

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 (seroresponse, vaccine response, seroconversion, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / data)	Log_{10}: Mean and standard deviation. Anti-Log_{10} (work on Log_{10} distribution, and anti-Log_{10} applied): Geometric mean (GM), 95% CI of the GM Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective

5.1.1.1 Hypotheses

Thirty days[a] after the administration of MenACYW conjugate vaccine or MENVEO®, the percentages of subjects who achieve an hSBA vaccine seroresponse[b] for meningococcal

[a] D30 (+14 days)

[b] The hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$
Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse in Group 1 and Group 2, respectively.

5.1.1.2 Statistical Methods

Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 percentages is > -10%, the inferiority assumption will be rejected. For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in percentages ($p_1 - p_2$) will be computed using the Wilson Score method without continuity correction (7).

Let $\hat{\theta} = p_1 - p_2$, then $L = \hat{\theta} - \delta$ and $U = \hat{\theta} + \varepsilon$ are respectively the lower and the upper limits of the CI, where:

$$\delta = Z_{0.025}\sqrt{\left\{\frac{l_1(1-l_1)}{n_1} + \frac{u_2(1-u_2)}{n_2}\right\}}$$

$$\varepsilon = Z_{0.025}\sqrt{\left\{\frac{l_2(1-l_2)}{n_2} + \frac{u_1(1-u_1)}{n_1}\right\}}$$

l_1 and u_1 are calculated from the CI of the single proportion in Group 1 given by:

$$\frac{(2n_1p_1 + Z^2_{0.025} \pm Z_{0.025}\sqrt{(Z^2_{0.025} + 4n_1p_1(1-p_1))})}{2(n_1 + Z^2_{0.025})}$$

l_2 and u_2 are calculated from the CI of the single proportion in Group 2 given by:

$$\frac{(2n_2p_2 + Z^2_{0.025} \pm Z_{0.025}\sqrt{(Z^2_{0.025} + 4n_2p_2(1-p_2))})}{2(n_2 + Z^2_{0.025})}$$

where $Z_{0.025}$ is the upper 97.5th percentile of the standard normal distribution.

The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Hypotheses

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

5.1.2.2 Statistical Methods

5.1.2.2.1 For Secondary Objective 1

Thirty days[a] after the administration of MenACYW conjugate vaccine or MENVEO®, the hSBA geometric mean titer ratio (GMTR) between Group 1 and Group 2 will be calculated and 95% CI will be provided as follows.

Logarithm transformation of the individual titers will be calculated. Assuming that individual $\log_{10}$(titer) is normally distributed, the 95% CI for the difference in $\log_{10}$(GMT) between Group 1 and Group 2 will be in the form:

$$\bar{X}_1 - \bar{X}_2 \pm t(1-\alpha/2, n_1+n_2-2)\cdot S\sqrt{1/n_1+1/n_2}$$

where $\bar{X}_i = \log_{10}(\text{GMT})$ is the mean of $\log_{10}$(titer) of Group i,

$S^2 = [(n_1-1)\,S_1^2 + (n_2-1)\,S_2^2] / (n_1+n_2-2)$ is the pooled sample variance,

n_i and S_i^2 are the sample size and sample variance of Group i,

$t(1-\alpha/2,\ n_1+n_2-2)$ is the 100(1-α/2) percentile of the t-distribution with degrees of freedom $df = n_1+n_2-2$.

The 95% CI for the hSBA GMTR between Group 1 and Group 2 will be formed by taking the antilogarithms of the lower and upper limits of the 95% CI for the difference in log(GMT) between both vaccine groups.

5.1.2.2.2 For Secondary Objective 2

Thirty days[a] after the administration of MenACYW conjugate vaccine or MENVEO® in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively, the hSBA GMTR between Group 1a and Group 2a, and between Group 1b and Group 2b will be calculated and 95% CI will be provided, respectively, as described in Section 5.1.2.2.1.

5.1.2.2.3 For Secondary Objective 3

Thirty days after the administration of MenACYW conjugate vaccine or MENVEO® in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively, the difference of hSBA vaccine

[a] D30 (+14 days)

seroresponse[a] rates between Group 1a and Group 2a, and between Group 1b and Group 2b will be calculated and 95% CI will be provided, respectively, as described in Section 5.1.1.2.

5.1.3 Statistical Methods for Observational Objectives

5.1.3.1 Hypothesis

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

5.1.3.2 Statistical Methods

5.1.3.2.1 Immunogenicity

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and MENVEO®.

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 log-normally distributed.

Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and MENVEO® treatment groups.

Descriptive analyses on A, C, Y, and W serogroups on D0 and D30 (+14 days) using hSBA will include but not be limited to:

- GMT and 95% CI in Group 1, Group 2, Group 1a, Group 1b, Group 2a, and Group 2b
- Titer distribution and RCDC
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI in Group 1, Group 2, Group 1a, Group 1b, Group 2a, and Group 2b
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI in Group 1, Group 2, Group 1a, Group 1b, Group 2a, and Group 2b
- Percentage of subjects with hSBA vaccine seroresponse[13] and 95% CI in Group 1, Group 2, Group 1a, Group 1b, Group 2a, and Group 2b

Descriptive analyses on A, C, Y, and W serogroups on D0 and D30 (+14 days) using rSBA will include but not be limited to:

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[a] The hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

- GMT and 95% CI in a subset of 200 subjects in Group 1 and Group 2, and in a subset of 100 subjects in Group 1a, Group 1b, Group 2a, and Group 2b
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI in a subset of 200 subjects in Group 1 and Group 2, and in a subset of 100 subjects in Group 1a, Group 1b, Group 2a, and Group 2b
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI in a subset of 200 subjects in Group 1 and Group 2, and in a subset of 100 subjects in Group 1a, Group 1b, Group 2a, and Group 2b
- Percentage of subjects with rSBA vaccine seroresponse[a] and 95% CI in a subset of 200 subjects in Group 1 and Group 2, and in a subset of 100 subjects in Group 1a, Group 1b, Group 2a, and Group 2b

5.1.3.2.2 Safety

Safety results in Section 4.3.2.2 will be described for subjects in all study groups. The main parameters for the safety endpoints will be described by 95% CIs (Clopper-Pearson method) (6). Analyses will contain at least the descriptions listed in Table 5.2:

Table 5.2: Statistical analyses for safety observational objective

Safety Events	Time and Group	Description
Immediate unsolicited systemic AE	Within 30 minutes after injection for all subjects in Groups 1 and 2 at D0	Percentage of subjects that have the event, MedDRA terms, intensity, relationship to vaccine, study discontinuation
Solicited injection site reactions	Up to 7 days after D0 for all subjects in Groups 1 and 2	Percentage of subjects that have the event, onset, duration, intensity, action taken, study discontinuation, temperature collection routes
Solicited systemic reactions	Up to 7 days after D0 for all subjects in Groups 1 and 2	
Unsolicited AE	Up to 30 days after D0 for all subjects in Groups 1 and 2	Percentage of subjects that have the event, MedDRA terms, onset, duration, intensity, relationship, action taken, study discontinuation

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

SAE [redacted]	Up to 6-month follow-up after D0 for all subjects in Groups 1 and 2	Percentage of subjects that have the event, MedDRA terms, onset, duration, relationship, seriousness criteria, outcome, study discontinuation
MAAE	Between Visit 1 and Visit 2 for all subjects in Groups 1 and 2 (as unsolicited AE) From Visit 2 to 6-month follow-up for all subjects in Groups 1 and 2	Percentage of subjects that have the event, MedDRA terms, onset, duration, intensity, relationship, action taken, study discontinuation

5.1.4 Complementary Output

Additional analyses by age group, gender, and race will be provided in Appendix 15 of the CSR.

Immunogenicity analyses:

- hSBA GMTs and 95% CI at each time point for each group – Per-Protocol Analysis Set
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA and 95% CI – Per-Protocol Analysis Set
- rSBA GMTs and 95% CI at each time point for each group – Per-Protocol Analysis Set
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by rSBA and 95% CI – Per-Protocol Analysis Set

Safety analyses:

Safety overview after injection –Safety Analysis Set

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. All subjects will be analyzed according to the treatment group to which they were randomized.

5.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received study vaccine[a] and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received.

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

5.2.3 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
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
- Subject did not provide the post-dose serology sample in the proper time window or a post-dose serology sample was not drawn. The time window will be defined as D30 to D44 (D30 +14 days) post-vaccination.
- Subject received a protocol-prohibited Category 2 or Category 3 therapy / medication / vaccine, as defined in Section 6.7 of the protocol.
- Subject's serology sample did not produce a valid test result
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

5.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

All safety analyses will be performed on the SafAS. Subjects will be analyzed according to the vaccine they actually received.

[a] For which safety data are scheduled to be collected

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 non-serious 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.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will be assumed to have occurred after the 30-minute surveillance period and will not be imputed. Such SAEs will not be considered as immediate.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop 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 visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) 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.

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

- 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

The derived endpoint of fold-rise is computed for extreme values, to minimize the numerator and maximizes the denominator as in Section 4.4.2.3.

5.3.3 Efficacy

Not applicable

5.4 Interim / Preliminary Analysis

Due to the possibility of delayed availability of the immunogenicity data generated using rSBA in a subset of subjects, and in order to not delay the analysis of safety data and available hSBA immunogenicity data, the analysis on rSBA immunogenicity data will be done separately when all rSBA testing has been completed. No statistical adjustment will be applied as there will be no repeat analysis of the same parameter and because the rSBA immunogenicity analysis is descriptive in nature.

5.5 Determination of Sample Size and Power Calculation

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]

[redacted]

5.6 Data Review for Statistical Purposes

Review of the data has been anticipated through the data review process led by data management before database lock. This review of the data will include a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

Not applicable

6 References List

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