NCT Number: NCT02842866

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adults Age 56 Years and Older

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® – A/C/Y/W-135 in adults ≥ 56 years of age in the United States.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET49
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
Indication For This Study:	MenACYW conjugate vaccine as a single dose for adults 56 years of age and older
Version and Date of the SAP core body part:	Version 1.0, 07 July 2016

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List of Abbreviations

AE	adverse event
AR	adverse reaction
BL	blood sample
CFU	colony-forming unit
CI	confidence interval
CRF	case report form
D	day
EDC	electronic data capture
FAS	full analysis set
GBS	Guillain-Barré syndrome
GMT	geometric mean titer
GMTR	geometric mean titer ratio
hSBA	serum bactericidal assay using human complement
ICH	International Conference on Harmonisation
IMD	invasive meningococcal disease
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
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 is a trial using MenACYW conjugate vaccine against invasive meningococcal disease (IMD). This Phase III trial 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 adults 56 years of age and older. The purpose of MET49 is to demonstrate non-inferiority of immunogenicity and evaluate the safety of a single dose of MenACYW conjugate vaccine compared to a single dose of Menomune®-A/C/Y/W-135 when given to adults 56 years of age and older.

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. The highest proportion of meningococcal cases was due to serogroup B in the population under 5 years of age. The highest proportion of serogroup C cases was observed in the population 25 to 44 years of age while the proportion of serogroup Y cases was highest in the population age 65 years and above. 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 1 year of age, 0.27 per 100,000 in 2 to 4 years of age, and 0.02 per 100,000 in children aged 5 to 17 years in 2013. The age specific incidence rate per 100,000 was 0.08 in 50 to 64 years, 0.03 in 65 to 74 years, 0.14 in 75 to 84 years, and 0.43 in 85 years 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: children as young as 6 weeks of age, adolescents, and adults including those 56 years of age and older.

MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. The current formulation has been evaluated in over 650 subjects (infants, toddlers, and adults > 55 years of age) in MET39 and MET44. There might be no direct benefit from receiving it. However, based on the data from studies MET28, MET32, MET39, and MET44, evaluation of the immunogenicity profile of MenACYW conjugate vaccine in different age groups showed that the majority of subjects developed seroprotective levels of antibodies after vaccination; the safety evaluation indicates that the vaccine is well-tolerated and no safety issues have been detected to date.

The purpose of MET49 is to demonstrate non-inferiority of immunogenicity and evaluate the safety of a single dose of MenACYW conjugate vaccine compared to a single dose of Menomune® – A/C/Y/W-135 in adults 56 years of age and older in the US.

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 those observed following the administration of a single dose of Menomune® – A/C/Y/W-135.

2.2 Secondary Objective

To compare the serum bactericidal assay 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 Menomune® – A/C/Y/W-135

2.3 Observational Objective

Immunogenicity

1) To describe antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135
2) To describe antibody titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using baby rabbit complement (rSBA) at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 in a subset of 100 subjects per treatment group.

Safety

To describe the safety profile of MenACYW conjugated vaccine compared to that of the licensed Menomune® – A/C/Y/W-135 after a single administration.

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 compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® - A/C/Y/W-135 in adults ≥ 56 years of age in the US.

Approximately 900 healthy adults will be randomized in a 1:1 ratio to the following groups:

- Group 1: MenACYW conjugate vaccine
- Group 2: Menomune® - A/C/Y/W-135

Enrollment will be stratified by age (see Table 3.1).

For subjects 56 to 64 years of age, 200 subjects will be enrolled in both Group 1 and Group 2.

For subjects 65 years of age and older, 250 subjects will be enrolled in both Group 1 and Group 2. These subjects will be further stratified into 2 groups as 65 to 74 years of age and 75 years of age and older. At least 25% of the 250 subjects will be enrolled in each of these age groups.

Table 3.1: Testing strategy for *N. meningitidis* serogroups ACYW

	ACYW serogroups tested by hSBA (all subjects)	**ACYW serogroups tested by rSBA (subset)**
Group 1		
56-64 years	200	50
≥ 65 years:	250	50
65-74 years	70-180	15-35
≥ 75 years	70-180	15-35
Group 2		
56-64 years	200	50
≥ 65 years:	250	50
65-74 years	70-180	15-35
≥ 75 years	70-180	15-35

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). Solicited AE information will be collected for 7 days after vaccination, unsolicited AE information will be collected from Visit 1 to D30 (Visit 2), and SAE information will be collected from D0 through D180 (+14 days) after vaccination. Information on medically-attended adverse events (MAAEs) will be collected 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

Vaccination

All subjects will receive a single dose of either MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 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 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).
- The subject will record information in a DC 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 will record information about any possible SAEs and MAAEs in a memory aid (MA) from Visit 2 until the 6 month (+14 days) telephone call.
- In addition, the subject will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- Staff will contact the subject by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the DC up to Visit 2 and to bring it back to Visit 2.
- The completed DC will be reviewed with the subject at Visit 2.
- Staff will contact the subject by telephone at 6 months (+14 days) after vaccination to review the MA and identify the occurrence of any MAAEs, as well as SAEs that have not been reported.

Table 3.2: Table of study procedures

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

Visit/Contact	**Visit 1**	**Telephone Call 1**	**Visit 2**	**Telephone Call 2**
Trial timelines (days)	D0	D08	D30	D180
Time windows (days)	--	+2 days	+14 days	+14 days
Informed consent form	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) 10 milliliter (mL)‡	BL1		BL2	
Vaccination§	X			
Immediate surveillance (30 minutes)	X			
DC provided	X			
Telephone call		X**		X††
Recording of solicited injection site and systemic reactions	D0 to D07			
Recording of unsolicited AEs	Visit 1 through Visit 2			
DC reviewed and collected			X	
Recording of MAAEs‡‡			After Visit 2 to Telephone Call 2	
Reporting of SAEs	To be reported throughout the study period			
Collection of reportable concomitant medications	X		X	
MA provided§§			X	
Termination of active phase of trial			X	
Completion of 6-month follow-up				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 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 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 will be collected from all subjects at D0.

§ Subjects will receive 1 dose of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135.

** 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 will find out whether the subject experienced any SAE not yet reported, and will remind the subject to continue using the DC up to Visit 2, to bring the DC to the study center at Visit 2, and confirm the date and time of Visit 2.

†† Staff will contact the subject by telephone at 6 months (180 days + 14 days) after D0 vaccination to identify the occurrence of any MAAEs or SAEs not yet reported.

‡‡ MAAEs that occur between the Visit 1 (D0) and Visit 2 will be recorded as unsolicited AEs.

§§The MA is used for the recording of SAEs and MAAEs. The site staff will make a telephone call to the subject to obtain the information 180 days (+ 14 days) after the vaccinations on D0. Since the timeframe between Visit 1 and Visit 2 (inclusive) will be captured in the DC, the MA will be used to collect SAE and MAAE data from Visit 2 to Telephone Call 2.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Primary Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days after vaccination

4.1.2 Primary Immunogenicity Endpoint Assessment Method

[redacted]

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Secondary Immunogenicity Endpoint

The secondary endpoint for immunogenicity is:

GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine and Menomune® – A/C/Y/W-135

4.2.2 Secondary Immunogenicity Endpoint Assessment Method

[redacted]

4.3 Observational Endpoints and Assessment Methods

4.3.1 Immunogenicity

4.3.1.1 Immunogenicity Endpoints

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135

4.3.1.2 Immunogenicity Assessment Methods

[redacted]

[redacted]

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

[a] T60: Time of incubation duration of 60 minutes

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:

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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, Guillain-Barré syndrome (GBS), new onset diabetes, or autoimmune disease.

- Symptom and
- Onset post-vaccination

e.g., injection site pain between D0 and D07 after vaccination, or headache between D0 and D07

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 D7 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 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.

Medically-Attended Adverse Events (MAAEs):

An MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject to seek unplanned medical advice at a physician's office or Emergency Department.

This definition excludes pre-planned medical office visits for routine 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 to 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 DC and electronic case report form [CRF]) injection site reactions occurring up to 7 days after vaccination.
- Occurrence, time to 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 DC and CRF) systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time to 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 occurring up to Visit 2.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the trial.
- Occurrence, nature (MedDRA preferred term), time to 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 about any solicited reactions and unsolicited AEs recorded in the DC, 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 protocol.

4.3.2.3.2 Reactogenicity (Solicited Reactions from Day 0 to Day 7 after Vaccination)

After vaccination, subjects will be provided with a safety DC, 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 DC 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 subject 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 will be contacted by telephone 8 days after vaccination to remind them to record all safety information in the DC.

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 DCs 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**
DC 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: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	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

CRF term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia
DC 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 / legally acceptable representatives 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:

Subjects 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 DC, and the highest temperature will be recorded by the site in the CRF. The preferred route for this trial is oral. Pre-vaccination temperature is also systematically collected by the Investigator in the source document. Tympanic thermometers must not be used.

4.3.2.3.3 Unsolicited Non-serious Adverse Events From Day 0 to Visit 2 After Vaccination

In addition to recording solicited reactions, subjects will be instructed to record any other medical events that may occur between Visit 1 and Visit 2 after vaccination. Space will be provided in the DC 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 subject 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)

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)

[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.

- 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 vaccination.

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.

4.3.2.3.5 Adverse Events of Special Interest

Not applicable.

4.3.2.3.6 Medically-Attended Adverse Events (MAAEs)

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 MA. 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]:

[a] ICH Guidelines, Clinical Safety Data Management E2A

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 Immunogenicity

4.4.1.1 Values for Analysis

In order to appropriately manage extreme values (< LLOQ and ≥ 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

4.4.1.2 Seroprotection

Not applicable

4.4.1.3 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.-

4.4.1.4 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:

- 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

4.4.2 Safety

4.4.2.1 Solicited Reactions

4.4.2.1.1 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/Pyrexia) with an investigator presence recorded as “No” and with all daily records missing then all daily intensities will be derived as None.
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 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).

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.

4.4.2.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.4.2.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.2.1.3 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 1 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.

4.4.2.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.2.1.1. 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.

4.4.2.1.5 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 4.4.2.1.1. 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.

4.4.2.1.6 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.

4.4.2.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.2.1.1 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.

4.4.2.2 Unsolicited Non-serious AEs

4.4.2.2.1 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."

4.4.2.2.2 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 the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm).

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.

4.4.2.2.3 Last Vaccination

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

4.4.2.2.4 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.

4.4.2.2.5 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.

4.4.2.3 SAEs

4.4.2.3.1 Last Vaccination

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

4.4.2.3.2 Time of Onset

Time of onset will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.2.2.4.

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.

4.4.2.3.3 Duration

Duration will be computed using the same methodology as for unsolicited non-serious AEs

described in Section 4.4.2.2.5.

4.4.2.4 Medically-Attended Adverse Events (MAAEs)

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. Unsolicited AEs that have action taken categories 2 or 3 will be summarized and presented as MAAEs between Visit 1 and Visit 2. After that MAAEs will be collected from Visit 2 to 6

months, as applicable. Calculation methods are the same as unsolicited non-serious AEs as described in Section 4.4.2.2.

4.4.2.5 Other Safety Endpoints

4.4.2.5.1 Pregnancy

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

4.4.2.5.2 Action Taken

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

4.4.2.5.3 Seriousness

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

4.4.2.5.4 Outcome

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

4.4.2.5.5 Causality

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

4.4.2.5.6 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
- 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

4.4.3 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

4.4.4.4 MAAEs from Visit 1 to Visit 2

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. The unsolicited AEs that have outcome categories 2 (health care provider contact) or 3 (Health care contact + Medication) will be summarized and presented as MAAEs during Visit 1and Visit 2.

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 after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135, the percentages of subjects who achieve an hSBA vaccine seroresponse[a] for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H_0): $p(_{G1}) - p(_{G2}) \leq -10\%$

[a] 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.

Alternative hypothesis (H_1): $p(G1) - p(G2) > -10\%$

where $p(G1)$ and $p(G2)$ are the percentages of subjects who achieve an hSBA seroresponse in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W will be tested separately.

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% CI of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected. For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions ($p_1 - p_2$) 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.

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

Thirty days after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135, the hSBA geometric mean titer ratio (GMTR) between Group 1 and Group 2 will be calculated and 95% CI will be provided.

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.

5.1.3 Statistical Methods for Observational Objective(s)

5.1.3.1 Hypotheses

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

5.1.3.1.1 For Immunogenicity Observational Objective 1

hSBA GMT will be calculated and summarized at each time point. For GMT parameters, 95% CIs of point estimates will be calculated using normal approximation assuming they are log normally distributed. Reverse cumulative distribution curves (RCDCs) of hSBA titer will be provided.

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

- GMT and 95% CI
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI

- Percentage of subjects with hSBA vaccine seroresponse[a]

5.1.3.1.2 For Immunogenicity Observational Objective 2

rSBA GMT will be calculated and summarized at D0 and D30 after vaccination. For GMT parameters, 95% CIs of point estimates will be calculated using normal approximation assuming they are log normally distributed. RCDCs of rSBA titer will be provided.

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

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

5.1.3.1.3 For Safety Observational Objective

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.

[a] 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.

[b] 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.

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	Proportion 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	Proportion of subjects that have the event, onset, duration, intensity, action taken, study discontinuation, temperature collection routes(if applicable)
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	Proportion of subjects that have the event, MedDRA terms, onset, duration, intensity, relationship, action taken, study discontinuation
SAE	Up to 6-month follow-up after D0 for all subjects in Groups 1 and 2	Proportion 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	Proportion 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 – Per-Protocol Analysis Set
- Percentage of subjects with hSBA vaccine seroresponse[a] and 95% CI – Per-Protocol Analysis Set

[a] 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.

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 Sets (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 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least 1 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 provide post-dose serology sample in the specified time window or a post-dose serology sample was not drawn. Time windows 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
- 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.

5.2.3 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. All subjects will have their safety analyzed according to the vaccine they actually received.

If the vaccine received by a subject does not correspond to any study group, the subject will be excluded from the SafAS. The corresponding safety data will be presented in separate listings.

5.2.4 Other Analysis Set

rSBA subset

Subjects who received the vaccine and provided a valid post-vaccination rSBA result.

5.2.5 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.

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 4.4.2.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.2.1.1. 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 4.4.1.3.

5.3.3 Efficacy

Not applicable

5.4 Interim / Preliminary Analysis

No interim or preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

5.5.1 Calculation of Sample Size

A total of 900 subjects will be enrolled.

[redacted]

5.5.2 Power Calculations for the Primary Objective

[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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