SANOFI PASTEUR

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Versus Nimenrix® or NeisVac-C® in Healthy Toddlers 12 to 23 Months of Age

Phase III, modified double-blind, randomized, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a single dose of MenACYW conjugate vaccine to a single dose of licensed NeisVac-C® or Nimenrix® in toddlers in Europe

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MEQ00065
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur 14 Espace Henry Vallée 69007, Lyon France
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular (IM)
Indication For This Study:	Toddlers aged 12 to 23 months
Version and Date of the SAP core body part:	Version 2.0, 16DEC2020

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List of Abbreviations

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

1 Introduction

This study will compare the immunogenicity of Serogroup C of a single dose of MenACYW conjugate vaccine to a single dose of licensed vaccines, NeisVac-C® (Meningococcal C –TT conjugate vaccine) or Nimenrix®(quadrivalent Meningococcal ACWY-TT conjugate vaccine) and describe the safety in healthy toddlers 12 to 23 months of age who are meningococcal vaccine naïve in Europe. The purpose of this study is to demonstrate that the immunogenicity of MenACYW conjugate vaccine is at least non-inferior to that of Nimenrix® (MenACWY-TT conjugate vaccine), and NeisVac-C®(meningococcal C (MenC)-TT conjugate vaccine), for serogroup C.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis (N. meningitidis)*, a Gram-negative diplococcus found exclusively in humans. It is associated with high morbidity and mortality. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial or purpuric rash. Invasive infection results in septicemia (~35%-40% of cases), meningitis (~50% of cases), or both. At least 12 different meningococcal serogroups have been classified based on the immunochemistry of the capsular polysaccharides (PS). Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, W, X and Y. Among them, serogroup C is responsible for large outbreaks.

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 second peak in the 15 to 19-year-old group. Most cases are due to serogroups B and C, but changing trends in the incidence of IMD have been reported in European countries in recent years with a decline of meningococcal B even in the countries without vaccination, reflecting the cyclical pattern of meningococcal disease incidence, and an increasing number of meningococcal W and Y cases. This situation has raised concern in some countries in the European Union (EU) to change (or consider to change) their vaccination strategies with a switch from Meningococcal C vaccination to Meningococcal ACWY vaccination in toddlers and/or in adolescents.

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

MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. MenACYW conjugate vaccine has been evaluated in over 7000 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in completed phase II and phase III studies. MenACYW conjugate vaccine is also being evaluated in ongoing Phase III studies concerning infants and toddlers: MET58, MET41, MET42, MET52, MET33, MET61, and MET62. Approximately 1500 toddlers (12 to 23 months of age) have received one dose of MenACYW conjugate vaccine in studies MET54, MET51 and MET57.

Based on the data generated from previous mentioned studies, the immunogenicity profile of the MenACYW conjugate vaccine in different age groups shows that the majority of subjects developed seroprotective levels of antibodies after vaccination. The safety evaluation indicates that the vaccine is well tolerated, and no unanticipated or new significant safety concerns have been identified in the clinical trials completed to date. The safety profile of MenACYW conjugate vaccine was comparable to that of the meningococcal ACWY licensed vaccines used as comparators in the completed studies. A number of licensed vaccines are, either targeting single serogroup (such as serogroup C vaccines) or a combination or multiserogroups (quadrivalent vaccines) which provide broad coverage and have the potential to protect individuals in countries with several predominant circulating serogroups (as currently observed in Europe with C serogroups and increasing W and Y serogroups).

Two meningococcal C (MenC) conjugate vaccines are currently licensed in European countries from 2 months of age. The MenC conjugate vaccines are made from capsular polysaccharide that has been extracted from cultures of capsular group C *Neisseria meningitidis*. The polysaccharide is linked (conjugated) to a carrier protein, either CRM_{197} (a non-toxic variant of diphtheria toxin) (Menjugate®) or tetanus toxoid (NeisVac-C®). The conjugation increases the immunogenicity, especially in young children in whom the plain polysaccharide vaccines are less immunogenic. The vaccination schedule and the number of vaccinations vary across the EU countries. In vaccinating countries, an infant may have 1 to 2 doses of meningococcal C conjugate vaccine during the first two years of life).

Quadrivalent meningococcal A, C, W and Y vaccines conjugated to CRM197 (Menveo®) or tetanus toxoid (Nimenrix®) are also licensed in Europe, with Nimenrix® approved for use from 6 weeks of age, while Menveo® is only licensed from 2 years of age.

The MenACYW conjugate vaccine is designed for the immunization of individuals of all ages (infants 6 weeks of age and older through and including older adults > 65 years of age) against IMD. The purpose of the vaccine is to provide broad coverage against circulating meningococcal strains from serogroups A, C, Y, and W. Compared to a previous Sanofi Pasteur meningococcal vaccine which is not licensed in Europe, Menactra®, the MenACYW conjugate vaccine is prepared by using tetanus toxoid as the carrier protein. Conjugation of PS antigens to a protein carrier can induce T-cell-dependent immune responses, which are anticipated to give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response.
Recommendations / National Immunization programs are heterogeneous in Europe, with some countries recommending only monovalent MenC vaccines in infancy/early childhood, while other countries have recently revised their recommendations to quadrivalent Men A, C, W, Y vaccines.

NeisVac-C® is considered the standard of care in several countries for meningococcal MenC vaccination in toddlers. So far none of the currently licensed meningococcal ACWY conjugate vaccines have been able to demonstrate non-inferiority of MenC immune response versus NeisVac-C®.

MenC has been one of the most important disease-causing serogroup in Europe and many countries in the world (e.g. Australia, Brazil, and Canada), and is still circulating. Therefore, health authorities are reluctant to use a ACWY vaccine of which the MenC component has not been shown to be non-inferior to monovalent MenC-TT vaccine. However, epidemiology is

changing with increasing notification rates of serogroups W & Y and a vaccine able to offer at least the same protection against MenC as monovalent MenC vaccine, while offering also a protection against other serogroups (W, Y) will provide an interesting option.

This study will aim to compare the immunogenicity of MenACYW conjugate vaccine versus quadrivalent MenACWY-TT conjugate vaccine, Nimenrix®, or versus monovalent MenC-TT conjugate vaccine, NeisVac-C®, and to describe the safety of one dose of MenACYW conjugate vaccine compared to one dose of Nimenrix® or to one dose of NeisVac-C® in toddlers 12 to 23 months of age.

High titers for serogroup C were observed with MenACYW conjugate vaccine vs Nimenrix® in MET54 Phase II study and MET51 Phase III study. While the non-inferiority of seroresponse as measured by hSBA versus Nimenrix® was demonstrated, the statistical superiority of the MenC response of MenACYW conjugate vaccine was not tested as a primary objective in MET51 study. The proposed study will address statistical superiority of serogroup C titers vs Nimenrix® as part of the primary objective; other serogroups (A, W, Y) will not be evaluated.

2 Trial Objectives

2.1 Primary Objectives

Immunogenicity

1) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by serum bactericidal assay using human complement (hSBA). If the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) is demonstrated, then
    1.1) to demonstrate the non-inferiority of the antibody response (geometric mean titers [GMT]) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then
    1.2) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. If the superiority of the antibody response (GMT) is demonstrated, then
    1.3) to demonstrate the superiority of the seroprotection rate to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA.
2) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by serum bactericidal assay using baby rabbit complement (rSBA). If the non-inferiority of the seroprotection rate is demonstrated, then
    2.1) to demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate

vaccine or NeisVac-C® as measured by rSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then

2.2) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by rSBA.

Overall, the primary objective for the study will be met if, objective 1) - non-inferiority of the seroprotection rate versus Nimenrix® as measured by hSBA, or objective 2) - non-inferiority of the seroprotection rate versus NeisVac-C® as measured by rSBA, is met.

2.2 Secondary Objectives

1) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA. If the non-inferiority of the seroprotection rate is demonstrated, then
   1.1) to demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then
      1.1.1) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA
2) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA. If the non-inferiority of the seroprotection rate is demonstrated, then
   2.1) to demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then
      2.1.1) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA.

Overall, the secondary objective for the study will be met if objective 1) - non-inferiority of the seroprotection rate versus Nimenrix® as measured by rSBA, or objective 2) - non-inferiority of the seroprotection rate versus NeisVac-C® as measured by hSBA, is met.

2.3 Observational Objectives

Immunogenicity

1) To describe the antibody response to meningococcal serogroup C before and 30 days (+14 days) after vaccination in each group using hSBA in toddlers

2) To describe the antibody response to meningococcal serogroup C before and 30 days (+14 days) after vaccination in each group using rSBA in toddlers

Safety

To describe the safety profile of MenACYW conjugate vaccine, Nimenrix® and NeisVac-C®.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase III, modified double-blind, randomized, active-controlled, multi-center trial to compare the immunogenicity for serogroup C of a single dose of MenACYW conjugate vaccine to a single dose of Nimenrix® vaccine or NeisVac-C® vaccine in toddlers, 12 to 23 months of age.

A total of 675 healthy toddlers aged 12 to 23 months who have not received any meningococcal vaccine during infancy, were initially planned to be enrolled . As a consequence of the COVID-19 pandemic, the study was put on hold and enrollment was paused on 17 March 2020. For ongoing subjects, approximately 30 subjects were identified to be excluded from the per protocol analysis set (PPAS) due to COVID-19 as they were unable to complete their follow-up visit as planned per the protocol. The sample size of the study has then been modified to replace these subjects, and approximately 705 subjects will now be enrolled and randomized to receive one dose of vaccine at Day (D) 0-Visit (V) 01, in one of the following 3 arms (1:1:1 ratio):

- Group 1: MenACYW conjugate vaccine
- Group 2: Nimenrix® vaccine (MenACWY-TT conjugate vaccine)
- Group 3: NeisVac-C® vaccine (MenC-TT conjugate vaccine)

All subjects will provide blood samples for immunogenicity assessment at V01 on D0 (pre-vaccination) and at V02 (30 to 44 days post-vaccination), which corresponds to the planned end of this study.

Solicited AE information will be collected for 7 days after vaccination, unsolicited AE information will be collected from D0 to D30, and SAE information, including adverse events of special interest (AESIs), will be collected throughout the trial.

3.2 Trial Plan

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

Vaccination

All subjects will receive a single dose of either MenACYW conjugate vaccine, NeisVac-C® or Nimenrix® on D0 (V01).

Blood Sampling

All subjects will provide a pre-vaccination blood sample at V01 (D0) and a post-vaccination sample at V02 (30 to 44 days after vaccination at V01).

Collection of safety data

- All subjects will be followed for safety from V01 on D0 to V02 after vaccination.
- All subjects will be observed for 30 minutes after vaccination and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited AEs in the electronic case report book (eCRB).
- The subject's parent or other legally acceptable representative will record information in a diary card (DC) about solicited reactions from D0 to D7 after vaccination and unsolicited AEs will be recorded from D0 to D30.
- Serious adverse events (SAEs, including adverse events of special interest [AESIs]) will be recorded in the DC throughout the study. The subject's parent / legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the study.
- Study site staff will contact subjects' parent / legally acceptable representative by telephone on 8 days (+2 days) after V01 to identify the occurrence of any SAEs (including AESIs) not yet reported and to remind them to complete the DC and bring it back to V02.
- The completed DC will be collected and reviewed with the subject's parent / legally acceptable representative at V02.

Table 3.1: Study procedures

Phase III Trial, 2 Visits, 1 Phone Call, 1 Vaccination, 2 Blood Samples, 30 to 44 Days' Duration per Subject

Visit/Contact	Visit 1	Telephone Call 1	Visit 2
Trial timelines (days)	D0	D8	D30
Time windows (days)	-	+2 days	+14 days
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Medical history	X		
Physical examination and Temperature	X		
Contact Interactive Response Technology (IRT) for randomization	X		
Review of temporary contraindications for blood sampling*			X
Blood sample (BL), 4 mL[†]	BL0001		BL0002
Vaccination[‡]	X		
Immediate surveillance (30 minutes)	X		
Diary card provided	X		
Telephone call		X[§]	
Recording of solicited injection site & systemic reactions	D0 to D7		
Recording of unsolicited AEs	D0 to D30		
Reporting of SAEs (including AESIs)	To be reported throughout the study period		
Diary card reviewed and collected			X
Collection of reportable concomitant medications	To be reported throughout the study period		
Termination record			X

* Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator was to postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0), when possible.

[†] Blood sample at Visit 1 was to be drawn before administration of the vaccine.

[‡] Subjects were to receive 1 dose of MenACYW conjugate vaccine or Nimenrix® or NeisVac-C®.

[§] This call is made 8 to 10 days after the vaccination at Visit 1. If D8 (+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 were to find out whether the subject experienced any SAE (including AESIs) not yet reported, and were to remind the subject's parent / legally acceptable representative 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.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

Immunogenicity

The endpoints for the evaluation of immunogenicity are:

1) Antibody against meningococcal serogroup C measured by hSBA, 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® (Group 1 versus Group 2)
   - Antibody titers
   - Antibody titers ≥ 1:8
2) Antibody against meningococcal serogroup C measured by rSBA, 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or NeisVac-C® (Group 1 versus Group 3)
   - Antibody titers
   - Antibody titers ≥ 1:8

4.2 Secondary Endpoints and Assessment Methods

Immunogenicity

The secondary endpoints for the evaluation of immunogenicity are:

1) Antibody against meningococcal serogroup C measured by rSBA, 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® (Group 1 versus Group 2):
   - Antibody titers
   - Antibody titers ≥ 1:8,
2) Antibody against meningococcal serogroup C measured by hSBA, 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or NeisVac-C® (Group 1 versus Group 3)
   - Antibody titers
   - Antibody titers ≥ 1:8

4.3 Observational Endpoints and Assessment Methods

Immunogenicity

The observational endpoints for the evaluation of immunogenicity are:

Observational Objective 1:

Antibody titers against meningococcal serogroup C measured by hSBA in each group:

- assessed before and at 30 days (+14 days) after vaccination
- ≥ 1:4 and ≥ 1:8, assessed at 30 days (+14 days) after vaccination
- post-vaccination / pre-vaccination titers ratio
- ≥4-fold rise from pre-vaccination to post-vaccination
- Vaccine seroresponse measured by hSBA, with seroresponse defined as:
  - for a subject with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16
  - for a subject with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer.

Observational Objective 2:

Antibody titers against meningococcal serogroup C measured by rSBA in each group:

- assessed before and at 30 days (+14 days) after vaccination
- ≥ 1:8 and ≥ 1:128, assessed before and at 30 days (+14 days) after vaccination
- post-vaccination / pre-vaccination titers ratio
- ≥4-fold rise from pre-vaccination to post-vaccination
- Vaccine seroresponse measured by rSBA, with seroresponse defined as:
  - for a subject with pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32
  - for subjects with pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer.

Safety

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

- Unsolicited systemic AEs reported in the 30 minutes following the vaccination including occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, relationship to vaccine and whether the AE led to early termination from the study.
- Solicited (pre-listed in the subject diary and the electronic CRF) injection site reactions and systemic reactions starting anytime from D0 (Day of vaccination) through D7 after the vaccination including: occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study.
- Unsolicited non-serious AEs between D0 and D30 including: occurrence, nature, time of onset, duration, intensity, action taken, relationship to vaccine, whether the AE led to early termination from the study and outcome
- SAEs (including AESIs) throughout the study, i.e., from D0 to Visit 2 including: occurrence, nature, time of onset, duration, seriousness criterion, relationship to vaccine, whether the AE led to early termination from the study, outcome

See Section 9.3.2 of the protocol for more details.

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.
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 safety 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 during the solicited period (D0 to D07) after vaccination.

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 during the solicited period (D0 to D07) after vaccination.

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the over the solicited period (D0 to D07) 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 – 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 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 at D07 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 (None) intensity event.

Grade 0 events will not be included in the analysis of the endpoint, and should be included in the listing "Unsolicited non-serious adverse events not included in the safety analysis."

4.4.1.2.2 Intensity

Intensity for unsolicited non-serious adverse event (AE) will be derived according to the following classification: Grade 0 (None), Grade 1, Grade 2, Grade 3, or Missing (Unknown).

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 than the intensity scales defined in the protocol 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

Since there is only one vaccination in this study, last vaccination before an 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 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 AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above (i.e., >30 days after vaccination) 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 (including AESIs)

4.4.1.3.1 Intensity

Intensity for SAEs will correspond to the value reported in the CRF.

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

4.4.1.3.2 Last Vaccination

Since there is only one vaccination in this study, last vaccination before a SAE is the study vaccination at V01.

4.4.1.3.3 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 (including AESIs) will be analyzed throughout the study using the following periods:

- Within 7 days after vaccination
- Within 30 days after vaccination
- During the study period: from D0 to last visit (i.e., all SAEs [including AESIs] occurred during the study)

An SAE (including AESI) 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 the safety analysis tables.

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

4.4.1.3.4 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 Other Safety Endpoints

4.4.1.4.1 Pregnancy

Not applicable.

4.4.1.4.2 Action Taken

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

4.4.1.4.3 Seriousness

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

4.4.1.4.4 Outcome

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

4.4.1.4.5 Causality

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

- Not related – The AE is clearly / most probably caused by other etiologies such as an 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 first vaccination (screening phase, if applicable)
- Related – There is a "reasonable possibility" that the AE was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship

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

For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor as either *not related* or *related.*

Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.4.6 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 "Adverse event" checked
- Safety overview table: A subject who has either on the termination form, the reason for early termination "Adverse event" checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has "Caused study discontinuation" or "Caused study termination" checked 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 non-serious, or SAE) that has "Caused study discontinuation" or "Caused study 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 (undetectable responses < the lower limit of quantitation [LLOQ] and ≥ the upper limit of quantitation [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2

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

4.4.2.2 Fold-rise

The derived endpoint of fold-rise is computed as follows:

- the ratio of post-vaccination computed value divided by baseline computed value

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

4.4.2.3 hSBA Vaccine Seroresponse

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

- if the pre-vaccination at baseline titer is < 1:8 and the post-vaccination titer ≥ 1:16
- or if the pre-vaccination at baseline titer is ≥ 1:8 and the post-vaccination is a ≥ 4-fold increase than the pre-vaccination titer.

4.4.2.4 rSBA Vaccine Seroresponse

The derived seroresponse indicator for rSBA will be "Yes":

- if the pre-vaccination at baseline titer is < 1:8 and the post-vaccination titer ≥ 1:32
- or if the pre-vaccination at baseline titer is ≥ 1:8 and the post-vaccination is a ≥ 4-fold increase than the baseline titer at post-vaccination

4.4.2.5 Efficacy

Not applicable

4.4.3 Derived Other Variables

4.4.3.1 Age for Demographics

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

4.4.3.2 Duration of a Subject in the Trial

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

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

4.4.3.3 Duration of the Study

The duration of the study is computed as follows:

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

5 Statistical Methods and Determination of Sample Size

[redacted]

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

[redacted]

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objectives

The immunogenicity of MenACYW conjugate vaccine serogroup C will be compared to that of Nimenrix® vaccine and to that of NeisVac-C® vaccine using sequential testing approaches.

The testing approach will be done in parallel and using a step by step approach for the 2 comparators (3 steps):

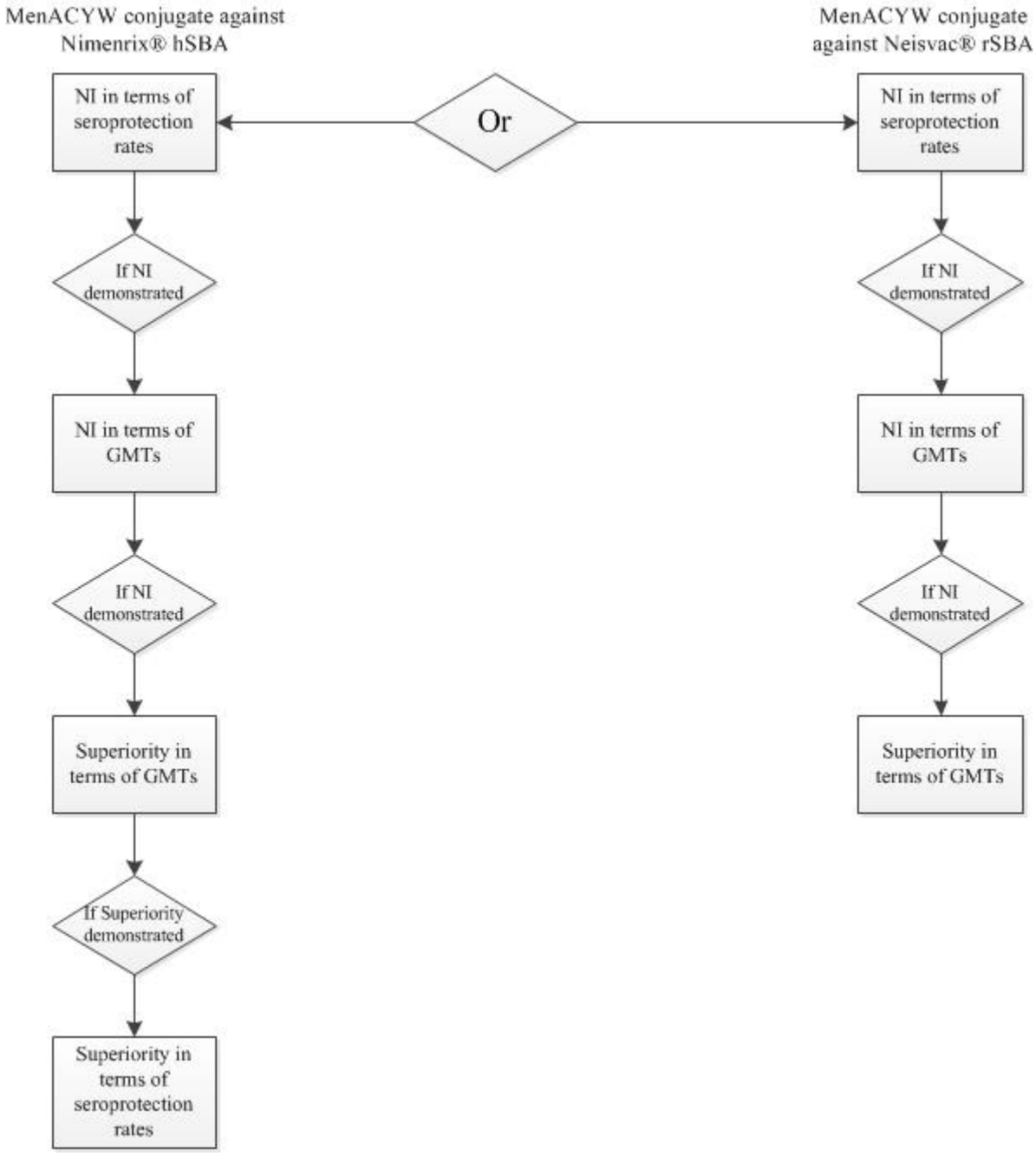
Nimenrix®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against Nimenrix® measured by hSBA is demonstrated then the non-inferiority using hSBA GMTs will be tested. If the non-inferiority using hSBA GMTs of MenACYW conjugate against Nimenrix® is demonstrated then the superiority using hSBA GMTs will be tested. If the superiority using hSBA GMTs is demonstrated then the superiority using hSBA seroprotection rates will be tested.

NeisVac-C®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against NeisVac-C® measured by rSBA is demonstrated then the non-inferiority using rSBA GMTs will be tested. And if the non-inferiority using rSBA GMTs is demonstrated then the superiority using rSBA GMTs will be tested.

Figure 1: Sequential statistical testing approach for primary objectives



To conclude, non-inferiority using seroprotection rates of MenACYW conjugate against Nimenrix® measured by hSBA or non-inferiority using seroprotection rates of MenACYW conjugate against NeisVac-C® measured by rSBA have to be demonstrated.

5.1.1.1 Hypotheses

Non-Inferiority

A non-inferiority testing approach will be used to compare post-vaccination (i.e., 30 days after the vaccination) seroprotection rates and GMTs of MenACYW conjugate vaccine to that of Nimenrix® and NeisVac-C®, using a two-sided 97.5% Confidence Interval (CI) with the following hypotheses:

For seroprotection rates, the objective is to demonstrate that thirty days after the administration of MenACYW conjugate vaccine, Nimenrix® or NeisVac-C®, the percentage of subjects who achieve an hSBA or rSBA titer ≥ 1:8 for meningococcal serogroups C in toddlers who received MenACYW conjugate vaccine (Group 1) is non-inferior to the corresponding percentage in toddlers who received Nimenrix® (Group 2) or NeisVac-C® (Group 3).

This primary objective will be met if the following null hypothesis is rejected for serogroup C:

$$H_0: \pi_{\text{MenACYW}} - \pi_{Comparator} \leq -0.1$$

$$H_1: \pi_{\text{MenACYW}} - \pi_{Comparator} > -0.1$$

where $\pi_{(\text{MenACYW})}$ and $\pi_{(\text{comparator})}$ are the percentages of subjects who achieve an hSBA or rSBA titer ≥ 1:8 in the MenACYW conjugate vaccine group and the comparator group (Nimenrix® or NeisVac-C®), respectively.

For GMTs, the objective is to demonstrate that thirty days after the administration of MenACYW conjugate vaccine, Nimenrix® or NeisVac-C®, the GMT against meningococcal serogroups C after MenACYW conjugate vaccine (Group 1) is non-inferior to the GMT after Nimenrix® injection in Group 2, or after NeisVac-C® (Group 3).

This objective will be met if the following null-hypothesis is rejected for serogroup C:

$$H_0: GMT_{\text{MenACYW}}/GMT_{Comparator} \leq 1/1.5$$

$$H_1: GMT_{\text{MenACYW}}/\ GMT_{Comparator} > 1/1.5$$

Superiority

If the non-inferiority testing succeeds then a superiority approach will be used to compare post-vaccination (i.e., 30 days after the vaccination) seroprotection rates and/or GMTs of MenACYW conjugate vaccine to that of Nimenrix® and NeisVac-C®, using a two-sided 97.5% CI with the following hypotheses:

For seroprotection rates, the objective is to demonstrate that thirty days after the administration of MenACYW conjugate vaccine, Nimenrix® or NeisVac-C®, the percentage of subjects who achieve an hSBA or rSBA titer ≥ 1:8 for meningococcal serogroups C in toddlers who received MenACYW conjugate vaccine (Group 1) is superior to the corresponding percentage in toddlers who received Nimenrix® (Group 2) or NeisVac-C® (Group 3).

This objective will be met if the following null hypothesis is rejected for serogroup C:

$$H_0: \pi_{\text{MenACYW}} - \pi_{Comparator} \leq 0$$

$$H_1: \pi_{\text{MenACYW}} - \pi_{Comparator} > 0$$

where $\pi_{(MenACYW)}$ and $\pi_{(comparator)}$ are the percentages of subjects who achieve an hSBA or rSBA titer ≥ 1:8 in the MenACYW conjugate vaccine group and the comparator group (Nimenrix® or NeisVac-C®), respectively.

For GMTs, the objective is to demonstrate that thirty days after the administration of MenACYW conjugate vaccine, Nimenrix® or NeisVac-C®, the GMT against meningococcal serogroups C after MenACYW conjugate vaccine (Group 1) is superior to the GMT after Nimenrix® injection in Group 2, or after NeisVac-C® (Group 3).

This objective will be met if the following null-hypothesis is rejected for serogroup C:

$$H_0: GMT_{\text{MenACYW}} / GMT_{Comparator} \leq 1$$

$$H_1: GMT_{\text{MenACYW}} / GMT_{Comparator} > 1$$

with:

- Comparator: Nimenrix® or NeisVac-C®
- π: seroprotection rates

5.1.1.2 Statistical Methods

For the seroprotection rates, the 97.5% CI of the difference in proportions will be computed using the Wilson Score method without continuity correction (Newcombe method).

For the GMTs, the two-sided 97.5% CI of the ratio of post-vaccination GMTs will be calculated first using normal approximation of log-transformed titers and then by taking the antilogarithms of the lower and upper limits of the provided 97.5% CI.

The non-inferiority will be demonstrated against seroprotection rates if the null hypothesis is rejected, i.e., if the lower limit of the two-sided 97.5% CI for the difference between the seroprotection rates is > -10%.

The non-inferiority will be demonstrated against GMTs if the null hypothesis is rejected, i.e., lower limit of the two-sided 97.5% CI for the ratio of GMTs > 1/1.5.

The superiority will be demonstrated against seroprotection rates if the null hypothesis is rejected, i.e., if the lower limit of the two-sided 97.5% CI for the difference between the seroprotection rates is > 0%.

The superiority will be demonstrated against GMTs if the null hypothesis is rejected, i.e., lower limit of the two-sided 97.5% CI for the ratio of GMTs > 1.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

The testing approach will be done in parallel and using a step by step approach for the 2 comparators (3 steps):

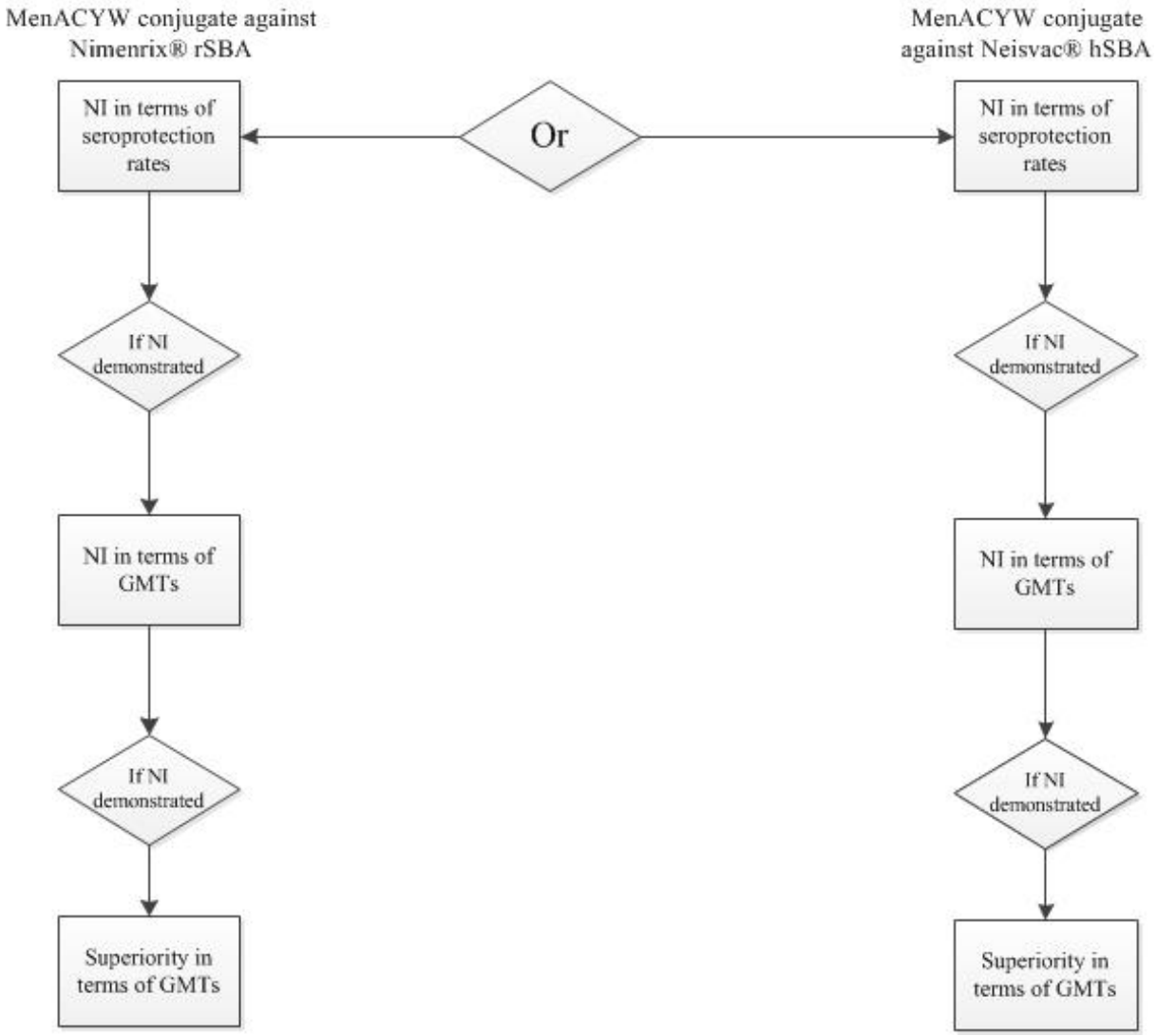
Nimenrix®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against Nimenrix® measured by rSBA is demonstrated then the non-inferiority using rSBA GMTs will be tested. If the non-inferiority using rSBA GMTs of MenACYW conjugate against Nimenrix® is demonstrated then the superiority using rSBA GMTs will be tested.

NeisVac-C®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against NeisVac-C® measured by hSBA is demonstrated then the non-inferiority using hSBA GMTs will be tested. And if the non-inferiority using hSBA GMTs is demonstrated then the superiority using hSBA GMTs will be tested.

Figure 2: Sequential statistical testing approach for secondary objectives



To conclude, non-inferiority using seroprotection rates of MenACYW conjugate vaccine against Nimenrix® measured by rSBA or non-inferiority using seroprotection rates of MenACYW conjugate vaccine against NeisVac-C® measured by hSBA have to be demonstrated.

5.1.2.1 Hypotheses

A similar statistical approach as for the primary objective will be used considering the rSBA antibody titers for Nimenrix® and hSBA antibody titers for NeisVac-C®.
Non-inferiority hypotheses will be similar as for the primary objective. Superiority will be tested only on GMTs, not on seroprotection rates.

5.1.2.2 Statistical Methods

Same methods will be used to computed 97.5% CI for seroprotection rate or GMTs.

5.1.3 Statistical Methods for Observational Objectives

Immunogenicity

The main parameters for observational objectives are:

Immunogenicity Observational Objective 1:

Descriptive analyses on meningococcal serogroup C measured by hSBA for all subjects in each group will include but not be limited to the following parameters:

- GMTs before and at 30 days (+14 days) after vaccination
- Percentage of subjects with antibody titers ≥ 1:4 and ≥ 1:8, assessed at baseline and 30 days (+14 days) after vaccination
- GMT ratio
- Percentage of subjects with a ≥4-fold rise from pre-vaccination to post-vaccination
- Vaccine seroresponse rate, with a seroresponse defined as:
    - for a subject with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16
    - for a subject with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer.
- Distribution titers

Immunogenicity Observational Objective 2:

Descriptive analyses on meningococcal serogroup C measured by rSBA for all subjects in each group will include but not be limited to the following parameters:

- GMTs before and at 30 days (+14 days) after vaccination
- Percentage of subjects with antibody titers ≥ 1:8 and ≥ 1:128, assessed before and at 30 days (+14 days) after vaccination in each group
- GMT ratio
- Percentage of subjects with a ≥4-fold rise from pre-vaccination to post-vaccination
- Vaccine seroresponse rate, with a seroresponse defined as:
    - for a subject with pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32

- for subjects with pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer.

- Distribution titers

Descriptive analyses will be done according to each vaccine group. The main parameters will be described with 95% CI using the exact binomial distribution (Clopper-Pearson method) for proportions and using the normal approximation of the Log_{10} concentrations/titers, followed by a back transformation for GMTs.

Reverse cumulative distribution curves (RCDCs) figures will also be provided for D0 and D30.

Safety Observational Objective:

For safety observational objectives results, the following parameters will be used in each group for the evaluation of safety: counts, percents and 95% CIs of point estimates (calculated using the exact binomial distribution [Clopper-Pearson method]) as well as number of AEs when considered of interest for each of the followings:

- Unsolicited systemic AEs reported in the 30 minutes following the vaccination
- Solicited injection site reactions and systemic reactions starting anytime from D0 through D7 after the vaccination
- Unsolicited non-serious AEs up to D30 after the vaccination
- SAEs (including AESIs) up to D30 after the vaccination and throughout the study, i.e., from D0 to Visit 2

Depending on the items, the parameters could be detailed according to:

Nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration / number of days of occurrence, intensity, relationship to vaccine, whether the AE led to early termination from the study, seriousness criterion, outcome.

5.2 Analysis Sets

Four main analysis sets will be used in the study: 2 full analysis set (hSBA FAS and rSBA FAS), 2 per protocol analysis sets (hSBA PPAS and rSBA PPAS) and the safety analysis set (SafAS).

5.2.1 Full Analysis Set

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

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

5.2.2 Per-Protocol Analysis Set

The PPAS are subsets of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from all 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 at V02 in the proper time window (i.e., D30+14 days) or the post-dose serology sample was not drawn.
- Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine
- Subject had other protocol violations or deviations that affected the subject's immune response, as determined by the clinical team before locking the database.

In addition to the reasons listed above, subjects will also be excluded from the hSBA PPAS if:

2.2) Subject post-dose serology sample at V02 did not produce a valid test result (i.e., hSBA result is missing or not reported)

And from the rSBA PPAS if:

2.3) Subject post-dose serology sample at V02 did not produce a valid test result (i.e., rSBA result is missing or not reported)

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

5.2.3 Safety Analysis Set

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

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

5.2.4 Populations Used in Analyses

The primary immunogenicity analyses will be performed on the hSBA PPAS for comparisons to Nimenrix® and on the rSBA PPAS for comparisons to NeisVac-C® and will be confirmed on the FAS.

The secondary immunogenicity analyses will be performed on the rSBA PPAS for comparisons to Nimenrix® and on the hSBA PPAS for comparisons to NeisVac-C® and will be confirmed on the FAS.

Observational objectives on immunogenicity will be performed on the PPASs and the FAS.

Observational objectives on safety will be performed on the SafAS.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

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

5.3.1.1 Immediate

For unsolicited 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 remain missing and 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.

5.3.1.6 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

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

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

Calculation of Sample Size:

To complete the primary objective a total of 675 subjects were initially planned to be enrolled according to a ratio 1:1:1 (MenACYW: Nimenrix®: NeisVac-C®).

This sample size will provide acceptable global powers considering an overall one-sided alpha of 2.5% (i.e., 1.25% adjusted alpha for each of the 2 main non-inferiority tested, then same level of alpha is used for the subsequent tests as a ranking testing strategy is used), a drop-out rate of 10% (i.e., 202 evaluable subjects per group, not taking into account the impact of COVID-19) and based on the following additional hypotheses:

Table 5.2: Statistical hypotheses and powers for the primary objective

Objective number	Step	Comparator	Statistical test	Endpoint	Ref. MenACYW vs Comparator	Clinical margin	Standard deviation (SD)	Individual power	Sequential Power
1	1	Nimenrix hSBA	NI	Seroprotection rates	98% vs 88%	10%		>99.9%	>99.9%
	2	Nimenrix hSBA	NI	GMTs	GMTR=1.5	1.5	0.5	>99.9%	>99.9%
	3	Nimenrix hSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	89.9%
	4	Nimenrix hSBA	Sup	Seroprotection rates	98% vs 88%	10%		95.8%	86.1%
2	1	Neisvac-C rSBA	NI	Seroprotection rates	98% vs 98%	10%		>99.9%	>99.9%
	2	Neisvac-C rSBA	NI	GMTs	GMTR=1	1.5	0.5	90.1%	90.1%
	3	Neisvac-C rSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	81.2%

NI: non-inferiority; Sup: superiority

GMTR: Geometric Mean of Titers ratios of MenACYW vs Comparator

One-sided Alpha of 1.25% used for all calculations

Sequential power correspond to the overall power of each step of the statistical tests to be performed

Reference seroresponse rates and SDs made from Phase II and III toddler studies MET51, MET32 and MET54.

In addition, considering such sample size will also provide acceptable global powers to achieve the secondary objective, considering an overall one-sided alpha of 2.5% (i.e., 1.25% adjusted alpha for each of the 2 main non-inferiority tested, then same level of alpha is used for the subsequent tests as a ranking testing strategy is used), an initial drop-out rate of 10% (not taking into account the impact of COVID-19) and based on the following additional hypotheses:

Table 5.3: Statistical hypotheses for the secondary objective

Objective number	Step	Comparator	Statistical test	Endpoint	Ref. MenACYW vs Comparator	Clinical margin	Standard deviation (SD)	Indivi-dual power	Sequential power
1	1	Nimenrix rSBA	NI	Seroprotection rates	98% vs 98%	10%		>99.9%	>99.9%
	2	Nimenrix rSBA	NI	GMTs	GMTR=1.5	1.5	0.5	>99.9%	>99.9%
	3	Nimenrix rSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	90.1%
2	1	Neisvac-C hSBA	NI	Seroprotection rates	98% vs 98%	10%		>99.9%	>99.9%
	2	Neisvac-C hSBA	NI	GMTs	GMTR=1	1.5	0.5	90.1%	90.1%
	3	Neisvac-C hSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	81.2%

NI: non-inferiority; Sup: superiority
GMTR: Geometric Mean of Titers ratios of MenACYW vs Comparator
One-sided Alpha of 1.25% used for all calculations
Sequential power corresponds to the sequential power of each step of the statistical tests to be performed
Reference seroresponse rates and SDs made from Phase II and III toddler studies MET51, MET32 and MET54.

As a consequence of the COVID-19 hold, approximately 30 subjects were identified to be excluded from the PPAS as they were unable to complete their follow-up visit as planned in the protocol. To maintain the planned study power and the randomization ratio, approximately 30 additional subjects are planned to be enrolled, with a planned final distribution of 235:235:235, the sample size of the study has then been modified to replace these subjects. Therefore, approximately 705 subjects will be enrolled.

5.6 Data Review for Statistical Purposes

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

5.7 Changes in the Conduct of the Trial or Planned Analyses

The definition of FAS was updated to be homogeneous with other MenQuadTT studies.

The titer distribution will be considered as a main parameter for observational analysis.

6 References List

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

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