NCT03691610

Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers

Phase III, modified double-blind, randomized, parallel group, active-controlled, multi-center study to compare the immunogenicity of MenACYW conjugate vaccine with that of MENVEO®, describe the immunogenicity of MenACYW conjugate vaccine and Menactra®, and describe the safety of MenACYW conjugate vaccine, MENVEO®, and Menactra® when administered in a 1 + 1 schedule concomitantly with routine pediatric vaccines to healthy infants and toddlers in the United States

Statistical Analysis Plan (SAP) – Core Body Part

Trial Code:	MET61
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	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 administered as a 2 dose series to healthy infants and toddlers
Version and Date of the SAP core body part:	Version 2.0 dated 11 December 2023

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CI	confidence interval
CRB	electronic case report book (a collection of all the case report forms for a subject)
CRF	electronic case report form (a single / specific case report form)
D	day
DC	diary card
DTaP	diphtheria, tetanus, acellular pertussis vaccine
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
GMC	geometric mean concentration
GMT	geometric mean titer
Hib	*Haemophilus influenzae* type b
hSBA	serum bactericidal assay using human complement
IMD	invasive meningococcal disease
IME	important medical event
IRT	interactive response technology
LLOQ	lower limit of quantitation
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MMR	measles, mumps, and rubella vaccine
PCV13	pneumococcal 13-valent conjugate vaccine
PPAS	per-protocol analysis set
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SMT	Safety Management Team
SOC	system organ class
TBD	to be determined
V	visit

1 Introduction

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 > 56 years of age) against invasive meningococcal disease (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 conjugate vaccine, Menactra®, the MenACYW conjugate vaccine is prepared 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. The program targets licensure of the MenACYW conjugate vaccine in many countries in North America, Europe, Latin America, Africa, the Middle East, and Asia Pacific.

The MenACYW conjugate vaccine is designed to cover broader age groups than those covered by Menomune® -A/C/Y/W-135 and Menactra®. Menactra® has been very successful since its licensure in 2005; however, it is not licensed in Europe and is not indicated in persons 8 months of age or younger or 56 years of age and older. While Menomune® -A/C/Y/W-135 and Menactra® are currently licensed in different parts of the world, the MenACYW conjugate vaccine is being developed by Sanofi Pasteur to ultimately replace Menomune® -A/C/Y/W-135 and Menactra® in the global market as a quadrivalent meningococcal conjugate vaccine indicated in infants/toddlers, children, adolescents, adults, and older adults > 56 years of age.

Meningococcal PS vaccines have two important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) PSs alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of PS vaccines in infants and children has been shown to be improved by conjugating the PSs to protein carriers. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of PS-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET39 and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above or subsequent trials using the final formulation or in the earlier trials.

MenACYW conjugate vaccine is being developed for the US infant/toddler population as a 4-dose (2, 4, 6, and 12 to 18 months of age) and 2-dose (6 to 7, and 12 to 13 months of age) series. Three Phase III studies (including MET61) will generate data to primarily support the licensing of the MenACYW conjugate vaccine in the US with an infant/toddler indication from 6 weeks of age. The purpose of the MET61 study is to evaluate the safety and immunogenicity of MenACYW conjugate vaccine and the comparator MENVEO® when administered in a 1 + 1 schedule and concomitantly with routine pediatric vaccines in healthy infants and toddlers in the US. This study will also describe the safety and immunogenicity of MenACYW conjugate vaccine and Menactra® when administered in a 1 +1 schedule to healthy toddlers in the US.

The MET61 study will generate data which will significantly contribute towards the overall safety database of the MenACYW conjugate vaccine in the US and in general.

2 Study Objectives

2.1 Primary Objective

To demonstrate the non-inferiority of the vaccine seroresponse[a] to meningococcal serogroups A, C, Y, and W following administration of 2 doses of MenACYW conjugate vaccine compared to 2 doses of MENVEO® when given concomitantly with routine pediatric vaccines to infants and toddlers at 6 to 7 months of age and 12 to 13 months of age

2.2 Secondary Objectives

Immunogenicity

1) To demonstrate the non-inferiority of the percentage of subjects with hSBA titers to meningococcal serogroups A, C, Y, and W ≥ 1:8 following administration of 2 doses of MenACYW conjugate vaccine compared to 2 doses of MENVEO® when given concomitantly with pediatric routine vaccines to infants and toddlers at 6 to 7 months of age and 12 to 13 months of age
2) To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine or MENVEO®
3) To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO® (in a subset of subjects)
4) To describe the antibody response against meningococcal serogroups A, C, Y, and W 6 months after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO® (in a subset of subjects)
5) To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine or Menactra®

2.3 Observational Objectives

Safety

1) To describe the safety profile of MenACYW conjugate vaccine and MENVEO® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers
2) To describe the safety profile of MenACYW conjugate vaccine and Menactra® administered in toddlers

[a] Vaccine seroresponse is measured with hSBA. 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 ≥ 4-fold greater than the pre-vaccination titer

3 Description of the Overall Study Design and Plan

3.1 Study Design

This is a Phase III, randomized, parallel group, active-controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and MENVEO® when administered in a 1 + 1 schedule and concomitantly with routine pediatric vaccines in healthy infants and toddlers in the US. This study will also describe the safety and immunogenicity of MenACYW conjugate vaccine and Menactra® when administered in a 1 + 1 schedule to healthy toddlers in the US. For each age group at enrollment, the study will have a modified double-blind design, i.e., modified double-blind between Group 1 and Group 2, and between Group 3 and Group 4.

A total of 1070 subjects will be enrolled. Approximately 870 healthy infants 6 to 7 months of age will be randomized 1:1 to 2 groups, and 200 healthy toddlers 17 to 19 months of age will be randomized 1:1 to 2 groups:

- Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
- Group 2 MENVEO® + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age
- Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age
- Group 4: Menactra® at 17 to 19 months of age and 20 to 23 months of age

All subjects in Group 1 and Group 2 will receive a dose of either MenACYW conjugate vaccine or MENVEO® with the following routine pediatric vaccines to ensure compliance with the Advisory Committee on Immunization Practices (ACIP) recommendations:

- Diphtheria, tetanus and acellular pertussis (DTaP) at 6 months of age
- Inactivated poliovirus (IPV) at 6 months of age
- *Haemophilus influenzae* type b (Hib) at 6 months of age. In children immunized with PedvaxHIB® at 2 and 4 months of age, a third dose of Hib vaccine at 6 months of age is not required.
- Pneumococcal 13-valent conjugate (Prevnar 13®, PCV13) at 6 and 13 months of age
- Rotavirus (RotaTeq®) at 6 months of age
- Hepatitis B at 6 months of age
- Measles, mumps, and rubella (M-M-R®II) at 12 months of age
- Varicella (Varivax®) at 12 months of age

The routine pediatric vaccines recommended at 6 months of age will be given as per standard of care during the first study visit (Visit 1) along with the corresponding study vaccine. The dose of Prevnar 13® and Hib (for children vaccinated with monovalent Hib vaccine at 2, 4, and 6 months of age) recommended in the second year of life may be given as per standard of care at the last study visit after completing all the study procedures (Visit 4). Routine pediatric vaccines

recommended at 6 months of age and the dose of Prevnar 13® recommended in the second year of life will not be provided by the Sponsor but procured by the sites as per their standard practices.

Blood Sampling

All subjects in Group 1 and Group 2 will provide 3 blood samples for immunogenicity assessment:

- A blood sample before the first study vaccination at Visit 1 (all subjects)
- A blood sample 30 days after administration of the first dose of MenACYW conjugate vaccine or MENVEO® at Visit 2 (only from approximately the first 50% of the subjects in Group 1 and Group 2)
- A blood sample before the 12-month vaccination at Visit 3 (only from the remaining approximately 50% of subjects in Group 1 and Group 2, who did not have a blood draw at Visit 2)
- A blood sample 30 days after administration of the second dose of MenACYW conjugate vaccine or MENVEO® at Visit 4 (all subjects in Group 1 and Group 2)

All subjects in Group 3 and Group 4 will provide 2 blood samples for immunogenicity assessment:

- A blood sample before the first study vaccination at Visit 1
- A blood sample 30 days after administration of the second dose of MenACYW conjugate vaccine or Menactra® at Visit 3

Collection of Safety Data

Safety data will be collected as follows: Immediate unsolicited systemic adverse event (AE) information will be collected within 30 minutes after each vaccination. Solicited AE information will be collected from D0 to D07 after each vaccination. Unsolicited AE information will be collected from D0 after each vaccination to the next study visit. SAE (including adverse event of special interest [AESI]) and medically-attended adverse event (MAAE) information will be collected throughout the study from Visit 1 until the end of the 6-month follow-up period after the last vaccinations.

3.2 Study Plan

Vaccination and blood sampling

Study vaccines will be administered and blood samples will be obtained following the schedules presented on Table 3.1 and Table 3.2.

All subjects will have at least 2 blood draws: at D0 (baseline, pre-vaccination) and at 30 days post vaccination 2. Fifty percent of subjects in Group 1 and Group 2 will also have an additional blood draw at Visit 2 (D30, post vaccination 1), the other 50% subjects will provide the blood draw at Visit 3 before the 2nd vaccination received.

A schedule of assessments and study vaccinations is provided on Table 3.3 and Table 3.4

Table 3.1: Vaccination and blood sampling schedule for Group 1 and 2

Age in months	**6 to 7 months**		**7 to 8 months**	**12 to 13 months**		**13 to 14 months**	
Visit #	Visit 1		Visit 2	Visit 3		Visit 4	
Procedure	**Blood Draw***	**Vaccines†**	**Blood Draw‡**	**Blood Draw§**	**Vaccines**	**Blood Draw**	**Vaccines****
Group 1	X	**MenACYW** DTaP IPV Hib PCV13 Rotavirus HB	X	X	**MenACYW** MMR Varicella	X	PCV13 Hib
Group 2	X	**MENVEO** DTaP IPV Hib PCV13 Rotavirus HB	X	X	**MENVEO** MMR Varicella	X	PCV13 Hib

* Blood will be drawn prior to vaccinations.
† Routine pediatric vaccines recommended at this age are to be given as per standard of care, and will not be provided by the Sponsor.
‡Blood sample at Visit 2 is applicable only to approximately the first 50% of the subjects in Group 1 and Group 2.
§Blood sample at Visit 3 is applicable only to the subjects in Group 1 and Group 2 who did not provide a blood sample at Visit 2 (approximately 50% in each group).
** PCV13 and Hib may be given as per standard of care outside of the study during the last study visit after completing all the study procedures (Visit 4). PCV13 and Hib will not be provided by the Sponsor.

Table 3.2: Vaccination and blood sampling schedule for Group 3 and 4

Age in months	**17-19 months**		**20-23 months**	**21-24 months**
Visit #	Visit 1		Visit 2	Visit 3
Procedure	**Blood Draw***	**Vaccine**	**Vaccine**	**Blood Draw**
Group 3	X	MenACYW	MenACYW	X
Group 4	X	Menactra	Menactra	X

*Blood will be drawn prior to vaccinations.

Table 3.3: Table of Study Procedures - Group 1 and 2

Phase III Study, 4 Visits, 2 Vaccinations visits, 3 Blood Samples, 4 Telephone Calls and 12 Months Duration per Subject

Visit (V) / Contact	**Visit 1**	**Telephone Call (TC) 1***	**Visit 2**	**TC 2†**	**Visit 3**	**TC 3***	**Visit 4**	**TC 4 Follow-up contact‡**
Approximate age of subjects	6 to 7 months§		7 to 8 months	11.5 to 12.5 months	12 to 13 months		13 to 14 months	18 to 19 months
Study timelines (days)	D0	Visit 1 +8 days	Visit 1 +30 days	Visit 3 -14 days	≥6 months post-Visit 1	Visit 3 +8 days	Visit 3 +30 days	Visit 3 +180 days
Time windows (days)		+2 days	+21 days			+2 days	+21 days	+30 days
Informed consent	X							
Inclusion/exclusion criteria	X							
Collection of demographic data	X							
Medical history	X							
Physical examination (including temperature measurement) **	X				X			
Contact interactive response technology (IRT) system for randomization/allocation of subject number/vaccine group assignment	X							
Review of temporary contraindications for blood sampling††	X		X		X		X	
Blood sampling (BL) (3 mL)	BL0001‡‡		BL0002A§§		BL0002B‡‡***		BL0003	
Review of warning and precautions to vaccinations	X				X			
Review of contraindications to subsequent vaccinations and conditions for withdrawal†††					X			
Contact IRT system for vaccine assignment	X				X			
Vaccination with MenACYW conjugate vaccine or MENVEO®	X				X			
Vaccination with routine pediatric vaccines‡‡‡	X§§§				X		X****	

Visit (V) / Contact	Visit 1	Telephone Call (TC) 1*	Visit 2	TC 2†	Visit 3	TC 3*	Visit 4	TC 4 Follow-up contact‡
Approximate age of subjects	6 to 7 months§		7 to 8 months	11.5 to 12.5 months	12 to 13 months		13 to 14 months	18 to 19 months
Study timelines (days)	D0	Visit 1 +8 days	Visit 1 +30 days	Visit 3 -14 days	≥6 months post-Visit 1	Visit 3 +8 days	Visit 3 +30 days	Visit 3 +180 days
Time windows (days)		+2 days	+21 days			+2 days	+21 days	+30 days
Immediate surveillance (30 minutes)	X				X			
Diary card provided	DC1		DC2		DC3			
Telephone Call		X		X		X		X
Diary card reviewed and collected			DC1		DC2		DC3	
Recording of solicited injection site and systemic reactions††††	X				X			
Recording of unsolicited adverse events	Recorded from D0 to D30 after each vaccination visit							
Reporting of SAEs (including AESIs) and MAAEs‡‡‡‡	To be reported throughout the study period							
Collection of reportable concomitant medications	X		X		X		X	
Memory Aid (MA) provided							X§§§§	
Completion at End of study							X	

*This call will be made 8 days after the respective vaccinations. If day 8 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 and/or MAAE not yet reported, and will remind the subject's parent / guardian to continue using the diary card, to bring the diary card to the study center at the next visit, and to confirm the date and time of the next visit.

†Staff will contact the subjects' parent / guardian by telephone within the 14 day time period before Visit 3 to remind them about the forthcoming study visit. If the subject's participation in the study is discontinued, the information recorded on the diary card will be reviewed at this time and the diary card will be retrieved by the site.

‡Staff will contact the subject's parent/ guardian by telephone at 6 months (+ 30 days) after the last vaccination visit to identify the occurrence of any SAEs (including any AESIs) and MAAEs not yet reported

§At Visit 1, subjects must be at least 24 weeks of age (168 days, the minimum age for the final dose of hepatitis B vaccine in the vaccine series) , and no more than 32 weeks of age (224 days, the maximum age for the 3rd dose of rotavirus vaccine administration).

**Physical examination should be performed as per routine standard of care. Temperature should be measured before vaccination and recorded in the source documents.

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

‡‡Blood sample will be drawn prior to vaccinations.

§§Blood sample at Visit 2 is applicable only to approximately the first 50% of the subjects in Group 1 and Group 2.

***Blood sample at Visit 3 is applicable only to the subjects in Group 1 and Group 2 who did not provide a blood sample at Visit 2 (approximately 50% of subjects in each group).
†††Physical examination should be performed on the basis of relevant medical history at the time of the visit according to the investigator's clinical judgment. Temperature should be measured before each vaccination and recorded in the source documents.
‡‡‡In children immunized with PedvaxHIB® at 2 and 4 months of age, a third dose of Hib vaccine at 6 months of age is not required.
§§§Routine pediatric vaccines recommended at this age are to be given as per standard of care, and will not be provided by the Sponsor.
****PCV13 will not be provided by the Sponsor. PCV13 may be given as per standard of care outside of the study during the last study visit after completing all the study procedures (Visit 4).
††††Solicited injection site and systemic reactions will be recorded from D0 through D07 after each vaccination visit.
‡‡‡‡AESIs will be collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner, and followed up until the end of the follow-up period or resolution, as per the assigned causality.
§§§§The memory aid will be used only for the recording of SAEs (including AESIs) and MAAEs from Visit 4 to the 6-month follow-up phone call (TC4).

Table 3.4: Table of Study Procedures – Group 3 and Group 4

Phase III Study, 3 Visits, 2 Vaccination visits, 2 Blood Samples, 10-month Duration per Subject

Visit / Contact	**Visit 1**	**TC 1***	**Visit 2**	**TC 2***	**Visit 3**	**TC 3 Follow-up contact†**
Approximate age of subjects	17 to 19 months		20 to 23 months		21 to 24 months	27 to 30 months
Study timelines (days)	D0	Visit 1 +8 days	≥3 months post-Visit 1	Visit 2 +8 days	Visit 2 +30 days	Visit 2 +180 days
Time windows (days)		+2 days		+2 days	+21 days	+30 days
Informed consent	X					
Inclusion/exclusion criteria	X					
Collection of demographic data	X					
Medical history	X					
Physical examination (including temperature)‡	X					
Randomization/allocation of subject number	X					
Review of temporary contraindications for blood sampling§	X				X	
Blood sampling (BL) (3 mL)	BL0001**				BL0002	
Review of warning and precautions to vaccinations	X		X			
Review of contraindications to subsequent vaccinations and conditions for withdrawal††			X			
Contact IRT system for vaccine assignment	X		X			
Vaccination with MenACYW conjugate vaccine or Menactra®	X		X			
Immediate surveillance (30 minutes)	X		X			
Diary card provided	DC1		DC2			
Telephone Call		X		X		X
Diary card reviewed and collected			DC1		DC2	
Recording of solicited injection site and systemic reactions‡‡	X		X			
Recording of unsolicited adverse events	Recorded from D0 to D30 after each vaccination visit					
Reporting of SAEs (including AESIs) and MAAEs§§	To be reported throughout the study period					
Collection of reportable concomitant medications	X		X		X	
MA provided					X	
Completion at End of study					X	

*This call will be made 8 days after the respective vaccinations. If day 8 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 and/or MAAE not yet reported, and will remind the subject's parent / guardian to continue using the diary card, to bring the diary card to the study center at the next visit, and to confirm the date and time of the next visit.

†Staff will contact the subject's parent / guardian by telephone at 6 months (+ 30 days) after the last vaccination visit to identify the occurrence of any SAEs (including any AESIs) and MAAEs not yet reported.

‡Physical examination should be performed as per routine standard of care. Temperature should be measured before each vaccination and recorded in the source documents.

§Should a subject receive oral or injectable antibiotic therapy within 3 days prior to any blood draw, the investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw. If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

**Blood sample will be drawn prior to vaccinations.

††Physical examination should be performed on the basis of relevant medical history at the time of the visit according to the investigator's clinical judgment. Temperature should be measured before vaccination and recorded in the source documents.

‡‡Solicited injection site and systemic reactions will be recorded from D0 through D07 after each vaccination visit.

§§AESIs will be collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Safety

There are no primary objectives for safety.

4.1.2 Immunogenicity

4.1.2.1 Immunogenicity Endpoint

The primary endpoint for the evaluation of immunogenicity is:

Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first study vaccination (Visit 1) and 30 days after the second dose of MenACYW conjugate vaccine or MENVEO® (Group 1 vs Group 2)

4.1.2.2 Immunogenicity Assessment Methods

The hSBA testing will be performed at GCI, Swiftwater, PA or at a qualified contract laboratory for GCI.

The assay method to be used is summarized below. Laboratory technicians conducting the immunogenicity assays will be blinded to the group to which each subject is assigned.

Antibodies to meningococcal antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in hSBA. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with human complement are added to the serum dilutions and allowed to incubate. After this incubation period, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight at 37°C with 5% carbon dioxide (CO_2). Bacterial colonies present in the wells are then counted. The endpoint titer is determined by the reciprocal serum dilution yielding ≥ 50% killing as compared to the mean of the complement control wells. The lower limit of quantitation (LLOQ) of the hSBA assay is a titer of 1:4.

4.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Safety

There are no secondary objectives for safety.

4.2.2 Immunogenicity

4.2.2.1 Immunogenicity Endpoints

The following serological endpoints will be assessed.

1) Meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:8 measured by hSBA 30 days after the second dose of MenACYW conjugate vaccine or MENVEO® (Group 1 vs Group 2)

2) 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine or MENVEO® (Group 1 and Group 2):

   - hSBA meningococcal serogroups A, C, Y, and W antibody titers
   - Geometric mean titers (GMTs) with 95% CI
   - Titer distribution and reverse cumulative distribution curves (RCDCs)
   - Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI

3) 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO® (Group 1 and Group 2):

   - hSBA meningococcal serogroups A, C, Y, and W antibody titers
   - GMTs with 95% CI
   - Titer distribution and RCDCs
   - Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI
   - Percentage of subjects with hSBA vaccine seroresponse and 95% CI

4) 6 months after the first vaccination at 6 to 7 months of age (pre-vaccination 2) with MenACYW conjugate vaccine or MENVEO® (Group 1 and Group 2):

   - hSBA meningococcal serogroups A, C, Y, and W antibody titers
   - GMTs with 95% CI
   - Titer distribution and RCDCs

- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse and 95% CI

5) 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine or Menactra® (Group 3 and Group 4):

- hSBA meningococcal serogroups A, C, Y, and W antibody titers
- GMTs with 95% CI
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse and 95% CI

4.2.2.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 4.1.2.2.

4.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Safety

4.3.1.1 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 in a clinical investigation subject administered a medicinal product and which does not necessarily 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 pre-existing condition
- 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 actions taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the study period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator 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 subject / event outcome or action criteria usually associated with events that pose a threat to a subject'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 (IME)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require

[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 outpatient 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.

intervention to prevent one of the other outcomes listed in the definition above. These IMEs 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, new-onset diabetes, or autoimmune disease.

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered an 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)

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the product administered) that occur within the first 30 minutes after vaccination.

Solicited Reaction:

A solicited reaction is an "expected" AR (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRB.

For injectable vaccines, solicited reactions can either be solicited injection site reactions or solicited systemic reactions.

Examples of solicited reactions include injection site tenderness or irritability occurring between D0 and D07 after vaccination.

By definition, solicited reactions are to be considered as being related to the product administered.

The assessment of these reactions by the Investigator is mandatory.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if vomiting between D0 and D07 is a solicited reaction (i.e., pre-listed in the protocol and CRB), then vomiting starting on D07 is a solicited reaction, whereas vomiting starting on D08 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

An injection site reaction is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions. They are considered to be related to the product administered.

Systemic AE:

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

Adverse Event of Special Interest (AESI):

An AESI is an event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (e.g., regulators) might also be warranted.

Medically-Attended Adverse Event (MAAE)

A MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject or subject's parent/guardian to seek unplanned medical advice at a health care provider's office or Emergency Department. This definition excludes pre-planned medical office visits for routine pediatric check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. Health care provider 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 health care provider 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.

4.3.1.2 Safety Endpoints

Table 4.1 below summarizes the safety data collection.

Table 4.1: Safety Endpoints and collection time window

Safety Endpoints	Immediate unsolicited systemic AEs	Solicited Injection site and systemic reactions	Unsolicited AEs	Medically attended AEs (MAAE)	Serious Adverse Events (SAEs)	Adverse Events of Special Interest (AESIs)§
Time window	30 minutes after each vaccination	Day 0 to Day 7 after each vaccination	Day 0 to Day 30 after each vaccination	Visit 1 to Day 180 (+30 days) Follow-up Telephone Contact after the last vaccination	Visit 1 to Day 180 (+30 days) Follow-up Telephone Contact after the last vaccination	Visit 1 to Day 180 (+30 days) Follow-up Telephone Contact after the last vaccination

AE – Adverse Event;
§ AESIs will be collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

4.3.1.3 Safety Assessment Methods

At each vaccination visit, the Investigator or a delegate will perform a physical examination on the basis of relevant medical history according to the Investigator's clinical judgment and will ask the parent / guardian about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

4.3.1.3.1 Immediate Post-vaccination Observation Period

Subjects will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination observation 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 CRB, as follows:

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected).
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination.
- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in the protocol.

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

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

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

The action(s) taken by the parent or guardian to treat and/or manage any solicited reactions will be classified in the CRB using the following list (all applicable items should be checked):

- None
- Medication
- Health care provider contact
- Hospitalized
- Discontinuation of study vaccination

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

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

Table 4.2 and Table 4.3 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 4.2: Solicited injection site reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	Injection site tenderness	Injection site erythema	Injection site swelling
MedDRA preferred term	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition	Pain when the injection site is touched or injected limb mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3: Cries when injected limb is mobilized, or the movement of the injected limb is reduced	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

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

Table 4.3: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA LLT)	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
MedDRA preferred term	Pyrexia	Vomiting	Crying	Somnolence	Decreased appetite	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥ 38.0°C (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F	Grade 1: 1 episode per 24 hours	Grade 1: < 1 hour	Grade 1: Sleepier than usual or less interested in surroundings	Grade 1: Eating less than normal	Grade 1: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	Grade 2: 2–5 episodes per 24 hours	Grade 2: 1–3 hours	Grade 2: Not interested in surroundings or did not wake up for a feed / meal	Grade 2: Missed 1 or 2 feeds / meals completely	Grade 2: Requiring increased attention
	Grade 3: > 39.5°C **or** > 103.1°F	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	Grade 3: Inconsolable

* For all reactions but fever, parents / guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

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

4.3.1.3.3 Unsolicited Adverse Events

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

Information on SAEs will be collected and assessed throughout the study, from Visit 1 until 6 months after the last vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRF. 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. In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE.

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

- Start and stop dates
- Intensity of the event:

For measurable unsolicited 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.

All other unsolicited AEs will be classified according to the following intensity scale:

- Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

- Whether the AE was related to the investigational product (for unsolicited systemic AEs)
- The Investigator will assess the causal relationship between the AE and the investigational product as either “Not related” or “Related”.
- Action taken for each AE (e.g., medication)

  The action(s) taken by the parent / guardian to treat and/or manage any unsolicited AEs will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination
- Whether the AE was serious

  For each SAE, the Investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)
- Whether the AE caused study discontinuation

4.3.1.3.4 Adverse Events of Special Interest

An AESI is defined as event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. The following AEs will be captured as AESIs throughout the study:

- Generalized seizures (febrile and non-febrile)
- Kawasaki disease
- Guillain-Barré syndrome
- Idiopathic thrombocytopenic purpura (ITP)

These events have been listed as AESIs based on the feedback received from the European Union regulators.

No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in the completed clinical trials. Because of their medical importance and to ensure expedited communication to the Sponsor, these AESIs are to be considered and collected as SAEs and reported to the Sponsor according to the procedure described in the protocol. Further instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

4.3.1.3.5 Medically-Attended Adverse Events

MAAE information will be collected throughout the study. MAAEs will be recorded as unsolicited AEs for up to D30 after each vaccination and as MAAEs until the next study visit on the appropriate diary cards. MAAEs that occur from D31 after the last vaccination visit until the 6-month follow up phone call will be recorded as such in the appropriate memory aid. An MAAE that occurs within the study period but meets the definition of an SAE should be reported only on the SAE Reporting Form. The Investigator will assess the causal relationship between the MAAE and the investigational or study product as "Not related" or "Related".

4.3.1.3.6 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the investigational 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.

AEs likely to be related to the product, whether serious or not, that persist at the end of the study 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 or the date of "chronicity" establishment.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.2 Solicited Reactions

4.4.2.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

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

1) Solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as "No" and with all daily records missing (unknown), then all daily intensities will be derived as None.
2) For non-measurable (NM) solicited reactions, the daily intensities will correspond to the 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 (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.

4.4.2.1.1 Maximum Intensity

Maximum overall intensity is derived from the daily intensities as described in Section 4.4.2.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.2.1.2 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 or Unknown: Missing presence

Subjects with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

The time period is displayed as D0-D3, D4-D7, D8 and later.

Note: solicited reactions with Missing presence will not be included in the safety analysis tables.

4.4.2.1.3 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.2.1. 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.

Time of onset is presented as D0-D3, D4-D7.

4.4.2.1.4 Number of Days of Occurence During the Solicited Period

Number of days of occurrence over the solicited period (D0 to D7) considered is derived from the daily intensities computed as described in Section 4.4.2.1. 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 (e.g, Grade 3) may also be derived.

4.4.2.1.5 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 after each vaccination 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:

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

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

4.4.2.1.6 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.2.1and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables)

4.4.2.2 Unsolicited 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 Grade 0 (None) intensity event.

Note: Unsolicited AEs with Grade 0 (None) intensity for a specific endpoint will not be included in the safety analysis tables.

4.4.2.2.2 Intensity

Intensity for unsolicited AE will be derived according to the following classification:

Grade 0 (None), Grade 1, Grade 2, Grade 3, or Unknown (or missing).

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule than the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

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

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

4.4.2.2.3 Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the CRF and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE
- If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE.

4.4.2.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination as described in Section 4.4.2.2.3:

Time of Onset = start date of the unsolicited AE - date of last vaccination before the unsolicited AE (if D0 is the first vaccination day).

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

The unsolicited AEs will be analyzed "Within 30 days" after each vaccination, which corresponds to AEs with a time of onset between day 0 and day 30.

Unsolicited AE that occurred before vaccination (negative time of onset) will not be included in analysis but will be listed separately.

Unsolicited AE which is non-serious, non-AESI and non-MAAE that occurred with a time of onset higher than defined above will not be included in analysis but will be listed separately.

- For unsolicited AE with missing day, month and year, the unsolicited AE will be classified as "Within 30 days"
- For unsolicited AE with partially missing start date, the partial available information will be used to determine if this AE is classified "Within 30 days" or "Not within 30 days". An AE will be categorized as "Not within 30 days" only if there is clear evidence from the

partially missing start date that this AE happens before the first vaccination or after the last vaccination + 30 days. In all other situations, this AE is considered as "Within 30 days". Situations may happen as:

- If the start date of AE has missing Day and non-missing Month and Year
  - If the "Month/Year of AE start date" < "Month/Year of first vaccination date", then it is clear that this unsolicited AE happened before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.
  - Else if the "Month/Year of last vaccination date" <= "Month/Year of AE start date" <= "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
  - Else if the "Month/Year of AE start date" > "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days". If the AE is non-serious, non-AESI and non-MAAE, then it will not be included in the analysis but will be listed separately.

- If the start date of AE has missing Day and Month and non-missing Year:
  - If the "Year of AE start date" < "Year of first vaccination date", then it is clear that this unsolicited AE happens before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.
  - Else if the "Year of last vaccination date" <= "Year of AE start date" <= "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
  - Else if the "Year of AE start date" > "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days". If the AE is non-serious, non-AESI and non-MAAE, then it will not be included in the analysis but will be listed separately.

A few examples of missing time of onset with start date of AE partially missing:

First injection date	Last injection date	Start date of the AE	Injection date + 30	Will be analyzed "Within 30 days" ?
16Oct2023	16Oct2023	Missing	N/A	Y
16Oct2023	16Oct2023	Sep2023	N/A	N
16Oct2023	16Oct2023	Oct2023	15Nov2023	Y
16Oct2023	16Oct2023	Nov2023	15Nov2023	Y
16Oct2023	16Oct2023	Dec2023	15Nov2023	N
05Jan2023	05Jan2023	2022	N/A	N

First injection date	Last injection date	Start date of the AE	Injection date + 30	Will be analyzed "Within 30 days" ?
16Oct2023	16Oct2023	2023	15Nov2023	Y
08Dec2023	08Dec2023	2024	07Jan2024	Y
16Oct2023	16Oct2023	2024	15Nov2023	N

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

Note: For project at a later stage, even if it's recommended to use the above rule, it's possible to follow the below rule, for homogeneity need:

The unsolicited AEs will be analyzed "Within 30 days" after each vaccination, which corresponds to Aes with a time of onset between day 0 and day 30 or missing .An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the section 4.4.2.2.3), so will be included in these tables.

4.4.2.2.5 Duration

Duration is derived from the start and stop dates of the unsolicited AE :

Stop date of unsolicited AE - start date of unsolicited 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 (including AESIs)

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

An event will be considered as ~~a~~ an AESI if "Yes" is checked for "Is the event an AESI?" in the CRF.

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

- Within 7 days after vaccination
- Within 30 days after vaccination
- During the study (i.e., all SAEs/AESI occurred during the study)

4.4.2.4 Medically-Attended Adverse Event (MAAE)

An event will be considered as an MAAE if "Yes" is checked for "Is the event an MAAE?" in the CRF.

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

- During the entire study period after any dose from D0 to last phone call (i.e., all MAAEs that occurred during the study)
- From Day 0 to Day 30 after each vaccination

A MAAE 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 mentioned above.

4.4.2.5 Other Safety Endpoints

4.4.2.5.1 Action Taken

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

4.4.2.5.2 Seriousness

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

4.4.2.5.3 Outcome

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

4.4.2.5.4 Causality

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

4.4.2.5.5 AEs Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Study" form question "What was the participant's status?" has "Adverse Event" checked.
- Safety overview table: A participant who has either on the "Completion at End of Study" form, question" What was the participant's status?" has "Adverse Event" checked or lists a solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.
- System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

4.4.3 Immunogenicity

4.4.3.1 Computed Values for Analysis

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

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

4.4.3.2 Seroprotection

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

4.4.3.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows. Generally, for extreme values, this algorithm minimizes the numerator and maximizes the denominator.

- If the baseline computed value is < LLOQ and the post-baseline computed value is < LLOQ, then the fold-rise is 1
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is ≥ LLOQ, then the fold-rise is post-baseline computed value / baseline computed value
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is < LLOQ, then the fold-rise is (LLOQ/2) / baseline computed value
- If the baseline computed value is < LLOQ and the post-baseline computed value is ≥ LLOQ, then the fold-rise is post-baseline computed value /LLOQ

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

4.4.3.4 A/C/Y/W Vaccine Seroresponse

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

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

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

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

4.4.4.2 Subject Duration

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

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

4.4.4.3 Duration of the Study

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

The duration of the study (including follow-up) is computed as follows: Maximum of all subjects (date of last visit, date of termination form, date of last follow-up contact) – minimum for all subjects (date of visit V01) +1

5 Statistical Methods and Determination of Sample Size

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

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 (1). 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 (seroprotection, vaccine seroresponse, 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 receiving MenACYW conjugate vaccine at 12 months of age, the hSBA vaccine seroresponse rates against meningococcal serogroups A, C, Y, and W in Group 1 is non-inferior to the corresponding hSBA vaccine seroresponse rates against meningococcal serogroups A, C, Y, and W in Group 2.
Null hypothesis (H0): $p_{(men, G1)} - p_{(men, G2)} \leq -10\%$
Alternative hypothesis (H1): $p_{(men, G1)} - p_{(men, G2)} > -10\%$
where $p_{(men, G1)}$ and $p_{(men, G2)}$ are the percentages of subjects who achieve hSBA vaccine seroresponse in Group 1 and Group 2, respectively.

5.1.1.2 Statistical Methods

Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 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 is computed using the Wilson Score method without continuity correction (2).

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 Objective(s)

5.1.2.1 Hypotheses for secondary objective 1

Thirty days after receiving MenACYW conjugate vaccine at 12 months of age, the percentage of subjects that achieve hSBA titers ≥ 1:8 for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H0): $p_{(men, G1)} - p_{(men, G2)} \leq -10\%$

Alternative hypothesis (H1): $p_{(men, G1)} - p_{(men, G2)} > -10\%$,

where $p_{(men, G1)}$ and $p_{(men, G2)}$ are the percentages of subjects who achieve hSBA ≥1:8 in Group 1 and Group 2 respectively.

5.1.2.2 Statistical Methods for secondary objective 1

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 non-inferiority hypotheses using the seroprotection rates, the CI of the difference in proportions is computed using the Wilson Score method without continuity correction in Section 5.1.1.2.

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

5.1.2.3 Statistical Methods for secondary objectives 2, 3, 4 and 5

No hypotheses will be tested. Descriptive statistics will be presented. The statistics presented on Table 5.1 will be produced as applicable. The 95% CIs of point estimates will be calculated using the exact binomial distribution (Clopper-Pearson method) for proportions (1). For GMs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

Descriptive statistics listed below will be provided for the immunogenicity endpoints in Section 4.2.2.1.

Table 5.2: Statistical analyses for immunogenicity objective(s)

Objectives	Group	Time point	description
Primary (hypothesis testing)	Group 1 and 2	D30 after 2nd vaccination	Vaccine seroresponse rate 30 days after 2nd vaccination
Secondary (hypothesis testing)	Group 1 and 2	D30 after 2nd vaccination	Seroprotection (titers >= 1:8) 30 days after 2nd vaccination
	Group 1 and 2	D0 (all subjects) D30 after 1st vaccination (50% subjects) 6 months after 1st vaccination (pre-vaccination 2 - the other 50% subjects) D30 after 2nd vaccination (all subjects)	hSBA GMT and 95% CI
			hSBA titer distribution and RCDC
			Proportion of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and 95% CI
			Proportion of subjects with hSBA titer ≥4-fold rise from baseline to the time point and 95% CI
			Proportion of subjects with hSBA vaccine seroresponse
	Group 3 and 4	At D0 D30 after the 2nd vaccination	hSBA GMT and 95% CI
			hSBA titer distribution and RCDC
			Proportion of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and 95% CI
			Proportion of subjects with hSBA titer ≥4-fold rise from D0 to 30 days after 2nd vaccination and 95% CI
			Proportion of subjects with hSBA vaccine seroresponse

5.1.3 Statistical Methods for Observational Objectives

No hypotheses will be tested. Descriptive statistics will be presented. The statistics presented on Table 5.1 will be produced as applicable. Safety results will be described for subjects in all study groups. The main parameters for the safety endpoints will be described by 95% CI using the exact binomial method (Clopper-Person method) (1).

5.1.4 Complementary Outputs

5.1.4.1 Sensitivity Analysis due to COVID-19 Pandemic

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

The subjects impacted by COVID-19 pandemic situation will be defined as the subjects with at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19 or who reported a 6-month follow up not completed in pandemic form. If more than 10% of subjects are impacted as per this definition, baseline and demographics characteristics, and the main immunogenicity and safety endpoints will also be summarized in the subsets of subjects impacted/ non-impacted subjects to assess the potential impact of COVID-19 situation on study outcome.

The assessment of the impact COVID-19 pandemic will be based on but not limited to the following analysis

- To summarize the impact of COVID-19 on the overall study conduct
  - Early termination due to COVID-19
  - Impact on visit conduct (visit not done, partially done, data collection method/procedure change)
  - Major and critical protocol deviations due to COVID-19

- To summarize disposition across study visits for subjects impacted/not impacted by COVID-19
- To summarize baseline demographics by randomized group for subjects impacted /not impacted by COVID-19
- To provide an individual listing of subjects impacted by COVID-19 and how they were impacted
- To provide a listing of visits impacted by COVID-19 and how they were impacted
- To assess the potential impact of COVID-19 on the main immunogenicity and safety endpoints in the subsets of impacted/non-impacted subjects

5.1.4.2 Subgroup Analysis

Additional subgroup analyses by gender and race based on PPAS will be provided for primary and main secondary immunogenicity endpoints.

The gender subgroup analyses will have two categories (Female and Male), and the race subgroup analyses will have four categories (White, Black, Asian, and Other).

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

- GMTs with 95% CI
- Percentage of subjects with titer ≥ 1:8 and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse and 95% CI

The safety overview will be also described by race and gender.

5.2 Analysis Sets

5.2.1 Safety Analysis Sets

There are 5 safety analysis sets defined as follows. Specific safety analysis set will be defined and used after each vaccination. All subjects will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the first dose.

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

5.2.1.1 Overall Safety Analysis Set for Any Dose

The overall SafAS is defined as those subjects who have received at least one dose of the study vaccines and have any safety data available. All subjects will have their safety analyzed after any dose according to the vaccine received at the first dose.

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

5.2.1.2 Safety Analysis Set for Vaccination at 6 Months of Age

The SafAS1 for vaccination at 6-7 months of age is defined as those subjects who have received the study vaccine at Visit 1 (Groups 1 and 2) around 6-7 months of age and have any safety data available. All subjects will have their safety analyzed after the Visit 1 dose according to the vaccines they actually received at Visit 1.

Safety data recorded for a vaccine received out of the protocol design at Visit 1 will be excluded from the analysis (and listed separately).

5.2.1.3 Safety Analysis Set for Vaccination at 12 Months of Age

The SafAS2 is defined as those subjects who have received the study vaccine at 12-13 months of age in Groups 1 and 2 at Visit 3 and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccines they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at that Visit 3 will be excluded from the analysis (and listed separately).

5.2.1.4 Safety Analysis Set for Vaccination at 17 Months of Age

The SafAS3 is defined as those subjects who have received the study vaccine at Visit 1 at 17-19 months of age in Groups 3 and 4 and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccines they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at that Visit 1 (Group 3 and 4) will be excluded from the analysis (and listed separately).

5.2.1.5 Safety Analysis Set for Vaccination at 20 Months of Age

The SafAS4 is defined as those subjects who have received the study vaccine at Visit 2 (Groups 3 and 4) at 20-23 months of age and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccine they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at that Visit 2 will be excluded from the analysis (and listed separately).

5.2.2 Full Analysis Set

There will be 3 FAS for this study.

FAS1 for infant vaccination:

- The FAS1 is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccine in infancy (< 12 months of age) and have a valid post vaccination serology result in infancy. All subjects will be analyzed according to the treatment group to which they were randomized.

FAS2 for second year of life vaccination:

- The FAS2 is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccine in the second year of life (≥ 12 months of age) and have a valid post-vaccination serology result in the second year of life. All subjects will be analyzed according to the treatment group to which they were randomized.

FAS3 for persistence after infant vaccination

- The FAS3 is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccine in infancy (< 12 months of age) and have a valid pre-vaccination serology result at visit 3. All subjects will be analyzed according to the treatment group to which they were randomized.

Immunogenicity analyses will be performed on the FAS for exploratory purposes.

5.2.3 Per-Protocol Analysis Set

Immunogenicity analyses will primarily be performed on PPAS. The PPAS is a subset of the FAS. There will be 3 PPAS corresponding to the 3 FASs.

- PPAS for infant vaccination (PPAS1) in Groups 1 and 2
- PPAS for second year of life vaccination (PPAS2) in Groups 1, 2, 3, and 4
- PPAS for persistence after infant vaccination (PPAS3) in Groups 1 and 2

5.2.3.1 Per-Protocol Analysis Set 1 (PPAS1)

Serology obtained 30 days after the vaccination visit at 6 months of age (post-vaccination 1) in a subset of subjects (Groups 1 and 2) for all antigens will be used for immunogenicity analyses of infant stage of study.

PPAS1 will be a subset of FAS1. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS1:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
    - Group 1 and Group 2
        - Visit 1: 24 to 32 weeks of age
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
    - Group 1 and Group 2
        - Blood Sampling 0002A: Visit 1 + 30 days (+21days)
- The serology sample did not produce a valid test results (i.e., results are missing)
- Subject received a protocol-prohibited therapy / medication / vaccine
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

Vaccine correctness required by the PPAS1 includes not only the dose of MenACYW conjugate vaccine or MENVEO® but also the concomitant vaccines (DTaP, IPV, Hib, PCV13, Rotavirus, hepatitis B) as scheduled.

In the event of a local or national immunization program with a pandemic influenza or coronavirus vaccine, subjects who receive 1 or more doses of a pandemic influenza or coronavirus vaccine at any time during the study will not be withdrawn from the study.

5.2.3.2 Per-Protocol Analysis Set 2 (PPAS2)

During the second year of life, the immunogenicity analyses for various antigens will be performed on serology obtained 30 days after the given antigen administration if blood collection is planned at that time.

PPAS2 will be a subset of FAS2. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule including the infant and the second year of the study:
  - Group 1 and Group 2: Up to 12-13 month vaccinations, including the infant schedule
  - Group 3 and Group 4: Up to 23 month vaccinations
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
  - Group 1 and Group 2
    - Visit 3: 12 to 13 months of age
  - Group 3 and Group 4
    - Visit 2: 20 to 23 months of age
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
  - Group 1 and Group 2
    - Blood Sampling 0003: Visit 4 (Visit 3 + 30 days [±21 days])
  - Group 3 and Group 4
    - Blood Sampling 0002: Visit 3 (Visit 2 + 30 days [±21 days])

- Subject received a protocol-prohibited therapy / medication / vaccine (reportable concomitant medication of category 2 and / or category 3)
- Subject had other protocol violations 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 PPAS if their serology sample did not produce a valid test result (i.e., results for all antigens are missing).

Vaccine correctness required by the PPAS2 includes not only the 2 doses of MenACYW conjugate vaccine, MENVEO®, or Menactra® but also, for subjects in groups 1 and 2, the concomitant vaccines (MMR, Varicella) as scheduled in the second year of life.

In the event of a local or national immunization program with a pandemic influenza vaccine or coronavirus vaccine, subjects who receive 1 or more doses of a pandemic influenza vaccine or coronavirus vaccine at any time during the study will not be withdrawn from the study.

5.2.3.3 Per-Protocol Analysis Set 3 (PPAS3)

Serology obtained at Visit3 for immunogenicity analysis for persistence 6 months after infant vaccination in a subset of subjects (Groups 1 and 2).

PPAS3 will be a subset of FAS3. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS3:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
    - Group 1 and Group 2
        - Visit 1: 24 to 32 weeks of age
- Subject did not provide a pre-dose 2 serology sample in the proper time window or a pre-dose 2 serology sample was not drawn at Visit 3
- The serology sample did not produce a valid test results at Visit 3 (i.e., results are missing)
- Subject received a protocol-prohibited therapy / medication / vaccine
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

Vaccine correctness required by the PPAS3 includes not only the dose of MenACYW conjugate vaccine or MENVEO® but also the concomitant vaccines (DTaP, IPV, Hib, PCV13, Rotavirus, hepatitis B) as scheduled.

In the event of a local or national immunization program with a pandemic influenza or coronavirus vaccine, subjects who receive 1 or more doses of a pandemic influenza or coronavirus vaccine at any time during the study will not be withdrawn from the study.

5.2.4 Populations Used in Analyses

The safety analysis will be performed on the Safety Analysis Set (SafAS, and SafAS1 through SafAS4). Subjects will be analyzed according to the vaccine(s) they actually received.

All immunogenicity analyses will be performed on the PPAS (PPAS1or PPAS2 or PPAS3) . Additional immunogenicity analyses will be performed for exploratory purposes on the FAS (FAS1 or FAS2 or FAS3). In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

5.2.5 Other Analysis Set(s)

Not applicable.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

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

5.3.1.1 Immediate

For unsolicited systemic AEs, a missing response to the “Immediate” field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

5.3.1.2 Causal relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.

The missing relationship to study procedures for SAEs will not be imputed.

5.3.1.3 Intensity

For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.3.1.4 Start Date and Stop Date

Missing or partially missing start dates or end dates for unsolicited Aes (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited Aes with missing time of onset will be included in analyses within or not within the defined time window (according to the section 4.4.2.2.4), according to the last vaccination (computed according to the section 4.4.2.2.3). If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

5.3.1.5 Action taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

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

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

Approximately 870 subjects will be enrolled in Group 1 and Group 2. An estimated around 20% to 30% and not higher than 40% of non-evaluable subjects will result in at least 522 subjects in the Per-Protocol population available for immunogenicity analyses. Group 1 will have 435 enrolled subjects and 261 evaluable subjects. Group 2 will have 435 enrolled subjects and 261 evaluable subjects. In addition, 200 subjects will be enrolled in Group 3 and Group 4.

In case of unexpected situations or any study hold resulting in an unexpected number of unevaluable subjects, total sample size may be increased to replace withdrawn, or unevaluable subjects.

For the Primary Objective:

Thirty days after the month 12 vaccination (after the second dose vaccination)

With 261 evaluable subjects in Group 1 and 261 evaluable subjects in Group 2, the study will have around 90.0% power by using Farrington and Manning's method to declare the non-inferiority of Group 1 vs Group 2.

Table 5.3: Power estimates to reject primary null hypothesis

Antigen	Endpoint	Estimated response (%)*	Non-inferiority margin	Power (%)
A	Seroresponse Rate	97.7	10%	100
C	Seroresponse Rate	97.8	10%	100
Y	Seroresponse Rate	93.3	10%	99.0
W	Seroresponse Rate	86.7	10%	91.0
Overall				90.0

Note: Evaluable subjects: Group 1 = 261 subjects; Group 2 = 261 subjects
*Estimated responses are based on results observed in MET39

For Secondary Objective 1:

Thirty days after the month 12 vaccination (after the second dose vaccination)

With 261 evaluable subjects in Group 1 and 261 evaluable subjects in Group 2, the study will have 100% power by using Farrington and Manning's method to declare the non-inferiority of Group 1 vs Group 2.

Table 5.4: Power estimates to reject the secondary null hypothesis

Antigen	Endpoint	Estimated response (%)*	Non-inferiority margin	Power (%)
A	% ≥1:8	>99.9	10%	100
C	% ≥1:8	>99.9	10%	100
Y	% ≥1:8	97.8	10%	100
W	% ≥1:8	97.8	10%	100
Overall				100

Note: Evaluable subjects: Group 1 = 261 subjects; Group 2 = 261 subjects
*Estimated responses are based on results observed in MET39

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

For MET61 study, concomitant medications category fields were inactivated, and concomitant medications were coded with WHODrug dictionary by the coding specialists.

Two additional population analysis sets for persistence immunogenicity analysis after infant vaccination (FAS3 and PPAS3) and the corresponding definitions were added as those populations of analysis were not pre-defined in the protocol.

Sections 4.4.2.2.3, 4.4.2.2.4 and 5.3.1.4 were updated according to new version of the Standard Safety Tables.

6 References List

1 Newcombe R.G., Two-sided confidence intervals for the single proportion: comparison of seven methods, Statistics in Medicine, (1998) 17, 857-872

2 Newcombe RG. Interval Estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998; 17(8):873-90