NCT03673462

A Randomized Study to Describe the Safety 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 describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the United States and Puerto Rico

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET41
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular
Indication For This Study:	MenACYW conjugate vaccine administered to healthy infants and toddlers at 2, 4, 6, and 12 months of age
Version and Date of the SAP core body part:	Version 1.0, 4Nov2020 Version 2.0. 15Mar2023

Table of Contents

List of Tables

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CSR	clinical study report
CRB	case report book
CI	confidence interval
D	day
DC	diary card
eCRF	electronic case report form
EDC	electronic data capture
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
IMD	invasive meningococcal disease
LLT	lowest level term
MA	memory aid
MAAEs	medically-attended adverse events
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
N.	*Neisseria*
NM	non-measurable
NR	not reportable
PT	preferred term
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	statistical analysis plan
SOC	system organ class (primary)
TLF	table(s), listing(s), and figure(s)
UAR	unexpected adverse reaction
V	visit

1 Introduction

This study (MET41) will evaluate the safety of a 4-dose series of the quadrivalent Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in children starting immunization at 6 weeks of age. The purpose of the MET41 study is to demonstrate that the safety profile of the MenACYW conjugate vaccine is similar to that of MENVEO® when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the United States (US) and Puerto Rico.

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

The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. Meningococcal disease occurs worldwide in both endemic and epidemic forms with seasonal variation. In Europe, the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 19 years old group. The highest incidence rate in Europe is caused by serogroup B, followed by C (5). In the US, the incidence rate of IMD was 0.14 per 100,000 in all ages; 0.83 per 100,000 in infants less than 1 year; 0.62 per 100,000 in toddlers 1 year of age; 0.27 per 100,000 in children 2 to 4 years of age; and 0.02 per 100,000 in children 5 to 17 years of age in 2013. The age specific incidence rate per 100,000 was 0.08 in adults 50 to 64 years of age, 0.03 in adults 65 to 74 years of age, 0.14 in adults 75 to 84 years of age, and 0.43 in adults 85 years of age and older in 2013 (6).

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

The MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 to < 40 years of age; and MET32, a Phase I/II study in toddlers. The formulation has been evaluated in around 7115 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in 10 completed studies: 4 Phase II studies in the US (MET39, MET44, MET50) and Finland (MET54); and 6 Phase III studies in the US (MET35, MET43, MET49, MET56), EU region (Spain, Germany, Hungary and Finland [MET51]), and in Thailand, South Korea, Russia, and Mexico (MET57). MenACYW conjugate vaccine was found to be well tolerated and no unanticipated or new significant safety concerns have been identified in the clinical trials completed to date.

The purpose of the MET41 study is to describe the safety profile of the MenACYW conjugate vaccine and the comparator MENVEO® when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the US. MET41 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 Objective

To describe the safety profile of MenACYW conjugate vaccine and MENVEO® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers. The endpoints for the study objective are presented in Section 4.1.1.2.

3 Description of the Overall Study Design and Plan

3.1 Study Design

This study is a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the US and Puerto Rico.

Approximately 3080 healthy infants aged ≥ 42 to ≤ 89 days will be randomized in a 3:1 ratio to the following 2 groups:

- **Group 1:** MenACYW conjugate vaccine + routine pediatric vaccines (N=2310)
- **Group 2:** MENVEO®+ routine pediatric vaccines (N=770)

All subjects will receive a dose of either MenACYW conjugate vaccine or MENVEO® with the following routine pediatric vaccines: Pentacel® (DTaP-IPV//Hib) at 2, 4, and 6 months of age; PREVNAR 13® (pneumococcal 13-valent conjugate vaccine; PCV13) at 2, 4, 6, and 12 months of age; RotaTeq® (rotavirus vaccine) at 2, 4, and 6 months of age; ENGERIX-B® (hepatitis B vaccine) at 2 and 6 months of age[a]; and M-M-R® II (measles, mumps, and rubella vaccine) and VARIVAX® (varicella vaccine) at 12 months of age. All subjects will complete the last study visit at 13 to 14 months of age. For all subjects, the 4th dose of Pentacel® should be administered by site personnel at 15 to 18 months of age as per standard practice. The 4th dose of Pentacel® will be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, to ensure compliance with the Advisory Committee on Immunization Practices (ACIP) recommendation.

Safety data will be collected as follows: Immediate unsolicited systemic AEs 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 events of special interest [AESIs]) 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 vaccination.

3.2 Study Plan

The schedule of assessments and study vaccinations is provided in the Table of Study Procedures (Table 3.1) and Table of Vaccination Schedule (Table 3.2).

[a] First dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment.

Vaccination

All subjects will receive a dose of either MenACYW conjugate vaccine or MENVEO® with routine pediatric vaccines at 2, 4, 6, and 12 months of age. All subjects will receive the routine pediatric vaccines at the approved ACIP recommended schedules: Pentacel® at 2, 4, and 6 months of age[a]; PREVNAR 13® at 2, 4, 6, and 12 months of age; RotaTeq® at 2, 4, and 6 months of age; ENGERIX-B® at 2 and 6 months of age[b]; and M-M-R® II and VARIVAX® at 12 months of age.

Study vaccines will be administered according to the following schedules:

Group 1: MenACYW conjugate vaccine and routine pediatric vaccines will be administered at 2, 4, 6, and 12 months of age.

Group 2: MENVEO® vaccine and routine pediatric vaccines will be administered at 2, 4, 6, and 12 months of age.

Blood sampling

No blood samples will be collected as this is a safety study.

Collection of safety data

- All subjects will be followed for safety from Visit 1 to 6 months after the last vaccinations at 12 months of age.
- All subjects will be observed for 30 minutes after each vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB).
- The subject's parent / guardian will record information in a diary card about solicited reactions from D0 to D07 after each vaccination and unsolicited AEs from D0 after each vaccination to the next study visit.
- SAEs (including AESIs) and MAAEs will be recorded throughout the study. The subject's parent / guardian will record information in a diary card about SAEs and MAAEs from Visit 1 to Visit 2, from Visit 2 to Visit 3, from Visit 3 to Visit 4, and from Visit 4 to Visit 5. SAEs and MAAEs will also be recorded in a memory aid from D31 after the last vaccination visit until the 6-month follow-up phone call.
- The subject's parent/ guardian will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- Site staff will contact the subjects' parent/ guardian by telephone 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAEs (including AESIs) and/or MAAEs not yet reported and to remind them to complete the diary card after each vaccination visit and to bring it back at the subsequent visit.
- The completed diary cards will each be collected and reviewed with the subject's parent/ guardian at the subsequent visit.

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[a] All subjects will complete the last study visit at 13 to 14 months of age. For all subjects, the 4th dose of Pentacel® should be administered by site personnel at 15 to 18 months of age as per standard practice. The 4th dose of Pentacel® will be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, as per ACIP recommendation.

[b] First dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment.

- Site staff will contact the subjects' parent/ guardian by telephone within 14 days before Visit 4 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 subject's parent / guardian will be asked to mail the diary card to the site.
- Site staff will contact the subjects' parent/ guardian by telephone at 6 months (+30 days) after the last vaccination visit to review the memory aid and identify the occurrence of any MAAEs, as well as SAEs (including AESIs) that have not been reported.

Table 3.3: Study Procedures

Phase III Study, 5 Visits, 4 Vaccination visits, 6 Telephone calls, 18 Vaccinations, 16-Months' Duration Per Subject

Visit/Contact	**Visit 1**	**Telephone Call (TC) 1**	**Visit 2**	**TC2**	**Visit 3***	**TC3**	**TC4**	**Visit 4†**	**TC5**	**Visit 5**	**TC6 Follow-up contact**
Approximate age of subject	2 months (42 to 89 days)	-	4 months	-	6 months (164 to 224 days)	-		12 months	-	13 months	18 months
Trial timelines (days)	D0	Visit 1 + 8 days	Visit 1 + 60 days	Visit 2 + 8 days	Visit 2 + 60 days	Visit 3 + 8 days	Visit 4 -14 days		Visit 4 + 8 days	Visit 4 + 30 days	Visit 4 + 180 days
Time windows (days)		+2 days	+14 days	+2 days	+14 days	+2 days			+2 days	+14 days	+30 days
Informed consent form signed and dated	X										
Inclusion/exclusion criteria	X										
Collection of demographic data	X										
Medical history	X										
Physical examination	X							X			
Temperature measurement	X		X		X			X			
Contact IRT system for randomization / allocation of subject number / vaccine group assignment	X										
Review of warnings and precautions to vaccinations	X		X		X			X			
Review of contraindications to subsequent vaccinations and conditions for withdrawal‡			X		X			X			
Contact IRT system for dose allocation for all vaccines			X		X			X			
Vaccination with MenACYW conjugate vaccine or MENVEO®	**X**		**X**		**X**			**X**			
Vaccination with routine pediatric vaccines§	**X**		**X**		**X**			**X**			
Immediate surveillance (30 minutes)	X		X		X			X			
Diary card (DC) provided	DC1		DC2		DC3			DC4			

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2	Visit 3*	TC3	TC4	Visit 4†	TC5	Visit 5	TC6 Follow-up contact
Telephone call		X**		X**		X**	X††		X**		X‡‡
Diary card reviewed and collected			DC1		DC2			DC3		DC4	
Recording of solicited injection site and systemic reactions§§	X		X		X			X			
Recording of unsolicited AEs		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		X	
Memory aid (MA) provided										MA†††	
Trial termination record (termination of active portion of the trial)										X	

* At Visit 3, subjects must be at least 24 weeks of age (the minimum age for the last dose of hepatitis B vaccine) and no more than 32 weeks of age (the maximum age for the last dose of rotavirus vaccine).

† At Visit 4, subjects must be 12 months of age, (from the day subjects turn 12 months of age until the day before turning 13 months of age).

‡ 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 needs to be measured before each vaccination and recorded in the source documents.

§ Routine pediatric vaccines at Visit 1: Pentacel®, PREVNAR 13®, RotaTeq®, ENGERIX-B®; at Visit 2: Pentacel®, PREVNAR 13®, and RotaTeq®; at Visit 3: Pentacel®, PREVNAR 13®, RotaTeq®, and ENGERIX-B®; at Visit 4: PREVNAR 13®, M-M-R® II, and VARIVAX®.

** This call is made 8 days after the respective vaccinations. If D08 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 (including AESIs) 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 confirm the date and time of the next visit.

†† Staff will contact the subjects' parent/ guardian by telephone within 14 days before Visit 4 (any time between 14 days and 1 day before Visit 4) 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 subject's parent / guardian will be asked to mail the diary card to 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. The final telephone call will continue until contact is made or 28 days have passed at which time the subject will be considered lost to follow-up.

§§ 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 is used only for the recording of SAEs (including AESIs) and MAAEs from Visit 5 to the 6-month follow-up phone call (TC6).

Table 3.4: Vaccination Schedule

Visit/Contact	Visit 1	Visit 2	Visit 3	Visit 4
Age of Subject	2 months	4 months	6 months	12 months
Group 1	MenACYW DTaP-IPV//Hib PCV13 Rotavirus Hep B	MenACYW DTaP-IPV//Hib PCV13 Rotavirus	MenACYW DTaP-IPV//Hib PCV13 Rotavirus Hep B	MenACYW PCV13 MMR Varicella
Group 2	MENVEO DTaP-IPV//Hib PCV13 Rotavirus Hep B	MENVEO DTaP-IPV//Hib PCV13 Rotavirus	MENVEO DTaP-IPV//Hib PCV13 Rotavirus Hep B	MENVEO PCV13 MMR Varicella

DTaP-IPV//Hib: Pentacel®; PCV13: PREVNAR 13®; Rotavirus: RotaTeq®; Hep B: ENGERIX-B®; MMR: M-M-R® II; Varicella: VARIVAX®

4 Endpoints and Assessment Methods

4.1 Observational Endpoints and Assessment Methods

4.1.1 Safety

4.1.1.1 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 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 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.

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.

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

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

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or 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.

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)

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

4.1.1.2 Safety Endpoints

The endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in

the subject's diary card and CRB) injection site reactions occurring up to D07 after each vaccination.

- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to D07 after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study for MAAEs throughout the trial, from Visit 1 to the 6-month follow-up contact after the last vaccination.

4.1.1.3 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.

4.1.1.3.1 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.

4.1.1.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 After Each Vaccination)

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

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

CRB term (MedDRA lowest level term [LLT])	**Injection site 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 4.2: 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	time : 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 or forehead skin thermometers must not be used.

4.1.1.3.3 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 the time of vaccination 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 case report form (CRF) and completing the appropriate Safety Complementary Information CRFs. 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. See the protocol for further details on SAE reporting.

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

- Start and stop dates[a]
- 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 (see Table 4.1 and Table 4.2).
  - 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

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

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", as described in Section 4.1.1.3.6.

  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

4.1.1.3.4 Adverse Events of Special Interest

An AESI is defined as an 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.

4.1.1.3.5 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 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 but not on the MAAE page of the CRB.

The Investigator will assess the causal relationship between the MAAE and the investigational or study product as either "Not related" or "Related", as described in Section 4.1.1.3.6.

4.1.1.3.6 Assessment of Causality

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

- Not related – The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination (screening phase, if applicable)
- Related – There is a "reasonable possibility" that the AE was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship

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

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.

4.2 Derived Endpoints: Calculation Methods

4.2.1 Safety

4.2.1.1 Solicited Reactions

4.2.1.1.1 Daily Intensity

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

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

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as "No" and with all daily records missing (Unknown), then all daily intensities will be derived as None.
2) For non-measurable (NM) solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions, the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (NM) is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator.

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.

4.2.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.1.1.3 Presence

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

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

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

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

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities as described in Section 4.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

4.2.1.1.5 Number of Days of Occurrence during the solicited period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

4.2.1.1.6 Overall Number of Days of Presence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

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

If the end date of the solicited reaction is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

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

4.2.1.2 Unsolicited AEs

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

4.2.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not Grade 0 intensity event.

Grade 0 events are not included in safety analysis but are included in separate listings.

4.2.1.2.2 Intensity

Intensity will be derived according to the following classification:

- None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the Section 5.3.1.2 for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but < 25 mm in adults). Intensity for the other unsolicited AEs will correspond to the value reported in the CRF. The maximum intensity corresponds to the highest intensity for a unique term.

4.2.1.2.3 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.

4.2.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination as described in Section 4.2.1.2.3

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

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

The unsolicited AEs will be analyzed "Within 30 days", which corresponds to AEs with a time of onset between 0 and 30 days after each vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination (computed according to Section 4.2.1.2.3), so will be included in these tables. Time of onset period is displayed as D0-D3, D4-D7, D8-D14, D15 or later, and Missing.

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

4.2.1.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE: Duration = End date of unsolicited AE - start date of unsolicited AE + 1.

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

4.2.1.3 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 an AESI if "Yes" is checked for "Is the event an AESI?" in the CRF.

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

- Within 7 days after vaccination
- Within 30 days after vaccination
- During the study (i.e., all SAEs occurred during the study), including the 6-month follow-up period

4.2.1.4 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.

MAAE will be analyzed during the following time periods:

- Within 7 days after vaccination
- Within 30 days after vaccination
- During the study (i.e., all MAAEs occurred during the study), including the 6-month follow-up period.

4.2.1.5 Other Safety Endpoints

4.2.1.5.1 Action Taken

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

4.2.1.5.2 Seriousness

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

4.2.1.5.3 Outcome

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

4.2.1.5.4 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.

4.2.1.5.5 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.

In general, the items that are counted are:

- Disposition table: A subject who on the "Completion at End of Study" form
- question "What was the participant's status?" has "Adverse Event" checked.
- Safety overview table: A subject who 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/Preferred Term (SOC/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.

4.2.2 Immunogenicity

Not applicable

4.2.3 Efficacy

Not applicable

4.2.4 Derived Other Variables

4.2.4.1 Age for Demographics

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

4.2.4.2 Subject Duration

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

> Maximum (Date of last visit, Date of term form) – (Date of V01) +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, Date of last follow-up contact) − (Date of V01) +1.

4.2.4.3 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 V01) +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 V01) +1

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software or later. The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics in Table 5.1 will be presented. The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (7)).

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.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for the Objectives

5.1.1.1 Hypotheses

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

5.1.1.2 Statistical Methods

5.1.1.2.1 Safety

Safety analysis will include but not be limited to the following:

- The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions occurring from D0 to D07 after each vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken.
- Immediate unsolicited systemic AEs and unsolicited AEs occurring up to D30 after each vaccination will be summarized.
- The number and percentage of subjects reporting any unsolicited non-serious AEs will be summarized by study group, intensity, time of onset period, duration, and by MedDRA preferred term and system organ class (SOC), as well as by relationship to the study vaccine.
- The number and percentage of subjects reporting at least one of any MAAEs will be summarized throughout the trial.
- The number and percentage of subjects reporting at least one of any SAEs will be summarized by study group, seriousness criterion, outcome, and by MedDRA preferred term and SOC, as well as by relationship to the study vaccine.
- The number and percentage of subjects reporting at least one of any AESIs will be summarized throughout the trial.

Safety results will be described for subjects in all study groups. The main parameters (e.g. percentage) for the safety endpoints will be described by 95% CIs using the exact binomial method (Clopper-Pearson method) (7).

Analyses will contain at least the descriptions listed in

Table 5.2

Table 5.2: Statistical analyses for safety observational objective

Safety Events	Time and Group	Description
Immediate unsolicited non-serious systemic AE	Within 30 minutes after each vaccination in Group1 and Group 2;	Percentage of subjects that have the event, MedDRA terms, intensity, relationship, study discontinuation, duration
Solicited injection site reactions	D0 to D7 after each vaccination in Group1 and Group 2;	Percentage of subjects that have the event, time of onset, duration, intensity, action taken, study discontinuation, number of days of occurrence, temperature collection routes
Solicited systemic reactions		
Unsolicited non-serious AE/AR	D0 to D30 after each vaccination in Group1 and Group 2;	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, study discontinuation
AEs leading to study discontinuation	D0 to D30 after each vaccination in Group 1 and Group 2; D31 to next visit after each vaccination in Group1 and Group 2; During the whole study in Group 1 and Group 2	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, outcome, study discontinuation
SAE (including AESI)	D0 to D7 after each vaccination in Group1 and Group 2; D0 to D30 after each vaccination in Group1 and Group 2; D31 to next visit after each vaccination in Group1 and Group 2; During the whole study in Group1 and Group 2	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, relationship, seriousness criteria, outcome, study discontinuation
MAAE	D0 to D30 after each vaccination in Group 1 and Group 2; D31 to next visit after each vaccination in Group1 and Group 2; During the whole study in Group 1 and Group 2	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, outcome, study discontinuation

5.1.1.2.2 Complementary Output

5.1.1.2.2.1 Subgroup Analysis by Race and Gender

Subgroup analyses by gender and race will be provided in Appendix 15 of the CSR.

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 subgroup analyses will be performed between Group 1 and Group 2 by gender and race.

Safety overview after any vaccine injection by gender– Overall Safety Analysis Set

Safety overview after vaccine injections at 2 months of age by gender – Safety Analysis Set 1

Safety overview after vaccine injections at 4 months of age by gender – Safety Analysis Set 2

Safety overview after vaccine injections at 6 months of age by gender – Safety Analysis Set 3

Safety overview after vaccine injections at 12 months of age by gender – Safety Analysis Set 4

Safety overview after vaccine injections by gender –Safety Analysis Set for All 4-Dose Vaccination

Safety overview after any vaccine injection by race – Overall Safety Analysis Set

Safety overview after vaccine injections at 2 months of age by race – Safety Analysis Set 1

Safety overview after vaccine injections at 4 months of age by race – Safety Analysis Set 2

Safety overview after vaccine injections at 6 months of age by race – Safety Analysis Set 3

Safety overview after vaccine injections at 12 months of age by race – Safety Analysis Set 4

Safety overview after vaccine injections by race – Safety Analysis Set for All 4-Dose Vaccination

5.1.1.2.2.2 Subgroup Analysis by Preterm and Full-term Birth

The following subgroup analyses by preterm (gestational age < 37 weeks) and full-term birth (gestational age ≥ 37 weeks) between Group 1 and Group 2 will be provided in Appendix 15 of the CSR.

Safety overview after any vaccine injection by the preterm and full-term birth – Overall Safety Analysis Set

Safety overview after vaccine injections by the preterm and full-term birth –Safety Analysis Set for All 4-Dose Vaccination

5.1.1.2.2.3 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. If more than 10% of subjects are impacted as per this definition, baseline and demographics characteristics, and main 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 safety endpoints in the subsets of impacted/non-impacted subjects

5.2 Analysis Sets

Six analysis sets will be used: the Overall Safety Analysis Set for any dose, Safety Analysis Set for vaccination 1 (SafAS1), Safety Analysis Set for vaccination 2 (SafAS2), Safety Analysis Set for vaccination 3 (SafAS3), Safety Analysis Set for vaccination 4 (SafAS4), and Safety Analysis Set for all 4-dose vaccinations.

5.2.1 Safety Analysis Set

The SafAS is defined as those subjects who have received at least 1 dose of the study vaccine(s)[a] and have any safety data available. Specific safety analysis will be defined and used after each vaccination. Safety analysis after all 4-dose vaccinations will also be conducted as well.

All subjects will have their safety analyzed after each dose according to the vaccine they actually received, after any dose, and after all 4 doses 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).

[a] A study vaccine is any vaccine that is administered as part of the study, including the investigational product (MenACYW conjugate vaccine), the control vaccine (Menveo), and the routine vaccines.

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 2 Months of Age

The SafAS1 is defined as those subjects who have received the study vaccine at Visit 1 around 2 months of age and have any safety data available. All subjects will have their safety analyzed after the Visit 1 dose according to the vaccine 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 4 Months of Age

The SafAS2 is defined as those subjects who have received the study vaccine at Visit 2 around 4 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 Visit 2 will be excluded from the analysis (and listed separately).

5.2.1.4 Safety Analysis Set for Vaccination at 6 Months of Age

The SafAS3 is defined as those subjects who have received the study vaccine at Visit 3 at around 6 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 this visit.

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

5.2.1.5 Safety Analysis Set for Vaccination at 12 Months of Age

The SafAS4 is defined as those subjects who have received the study vaccine at Visit 4 at around 12 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 Visit 4 will be excluded from the analysis (and listed separately).

5.2.1.6 Safety Analysis Set for all 4-dose Vaccinations

The SafAS for all 4-dose vaccinations is defined as those subjects who have received all 4 doses of the study vaccine (3 doses in infancy and 1 dose in the second year of life at 12 months of age) and have any safety data available. All 4-dose vaccinations received in a series should be either all MenACYW conjugate vaccine or all MENVEO®.

Safety data recorded for subjects not receiving all 4 doses of MenACYW or MENVEO® will be excluded from the analysis (and listed separately).

5.2.2 Populations Used in Analyses

The safety analysis will be performed on the Overall Safety Analysis Set for any dose, SafAS1 through SafAS4, and Safety Analysis Set for all 4-dose Vaccinations. Subjects will be analyzed according to the vaccine they actually received.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

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

5.3.1.1 Immediate

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

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

5.3.1.2 Causality

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 Measurements

Partially missing temperatures will be handled as described in Section 4.2.1.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and End Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.1.6 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

Not applicable

5.3.3 Efficacy

Not applicable

5.4 Interim / Preliminary Analysis

No interim or preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

The sample size of this study was chosen to provide safety data; it is not intended for the purposes of hypothesis testing. No formal sample size calculation is performed.

Though there are no statistically powered hypotheses, the overall study cohort of 3080 subjects will provide a probability of approximately 95% of observing any AE with a true incidence of 0.15%. In the treatment arm with 2310 subjects, there is a probability of approximately 95% of observing any AE with a true incidence of 0.2%.

5.6 Data Review for Statistical Purposes

Reviews of the data are anticipated through the data review process led by Data Management before database lock. This review of the data will include a statistical review.

In addition, an internal Safety Management Team (SMT) will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns.

5.7 Changes in the Conduct of the Study or Planned Analyses

For MET41 study, concomitant medications category fields were inactivated, and concomitant medications were coded with WHODrug dictionary by the coding specialists.

6 References List

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