Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Healthy Adults, Adolescents, and Children, in India and Healthy Adolescents and Children in the Republic of South Africa

Phase III, modified double-blind, randomized, parallel-group, active-controlled, step-wise, multi-center trial to compare and describe the immunogenicity and safety of MenACYW conjugate vaccine when administered as a single dose in healthy adults, adolescents, and children in India and a modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare and describe the immunogenicity and safety of MenACYW conjugate vaccine when administered as a single dose in healthy adolescents and children in the Republic of South Africa.

Statistical Analysis Plan (SAP) - Core Body Part

NCT Number: NCT04143061

Trial Code:	MET55
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, W, and Y) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular (IM)
Indication For This Study:	MenACYW conjugate vaccine administered as a single dose to healthy adults, adolescents, and children in India and healthy adolescents and children in the Republic of South Africa
Version and Date of the SAP core body part:	This SAP contains analyses planned in the CSR, version 1.0, 23Nov2023

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List of Abbreviations

Ab	antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CDM	Clinical Data Management
CI	confidence interval
CTL	Clinical Team Leader
CTM	Clinical Trial Manager
CSR	clinical study report
D	day
DC	diary card
dil	dilution
eCRF	electronic case report form
EDC	electronic data capture
EIA	enzyme immunosorbent assay
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
EDC	electronic data capture
EU	ELISA or EIA unit
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM	geometric mean
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
ITT	intent-to-treat
IU	international unit
IVRS	interactive voice response system
IWRS	interactive web response system
LLOD	lower limit of detection
LLOQ	lower limit of quantification
LLN	lower limit of normal

MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NSAID	non-steroidal anti-inflammatory drug
OPV	oral poliovirus vaccine
PC	phone call
PP	per-protocol analysis set
PSO	Product Safety Officer
PT	preferred term
PV	Pharmacovigilance
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SC	screening
SD	standard deviation
SOC	system organ class (primary)
TLF	table(s), listing(s), and figure(s)
ULOD	upper limit of detection
ULOQ	upper limit of quantification
ULN	upper limit of normal
V	visit
Vac	vaccination
WHO	World Health Organization

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 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 polysaccharide 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 polysaccharide vaccines have two important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) polysaccharides alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of polysaccharide vaccines in infants and children has been shown to be improved by conjugating the polysaccharides 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 polysaccharide-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) and the recent Phase III studies 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 trials using the final formulation or in the earlier trials.

The purpose of the MET55 study is to compare and describe the immunogenicity and safety of MenACYW conjugate vaccine when administered as a single dose in healthy adults, adolescents, and children in India and healthy adolescents and children in the RSA.

2 Trial Objectives

2.1 Primary Objective

To demonstrate the non-inferiority of immunogenicity of a single dose of MenACYW conjugate vaccine compared to Menactra® in adolescents and children aged 2 to 17 years in terms of serum bactericidal assay using human complement (hSBA) titers.

2.2 Secondary Objectives

1) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in adults aged 18 to 55 years in India
2) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years in India
3) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India and RSA
4) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India
5) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in RSA

2.3 Observational Objectives

Immunogenicity

To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in the children and adolescents aged 2 to 17 years by age groups (2 to 9 years of age and 10 to 17 years of age) in India and RSA combined and separated by India only or RSA only

Safety

1) To describe the safety profile of MenACYW conjugate vaccine and that of licensed Menactra® in adults aged 18 to 55 years in India
2) To describe the safety profile of MenACYW conjugate vaccine and that of licensed Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years in India
3) To describe the safety profile of MenACYW conjugate vaccine and that of licensed Menactra® in children and adolescents aged 2 to 17 years in India and RSA

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This study will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, step-wise, multi-center trial to compare and describe the immunogenicity and safety of MenACYW conjugate vaccine when administered as a single dose in healthy adults, adolescents, and children in India and a modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare and describe the immunogenicity and safety on MenACYW conjugate vaccine when administered a single dose in healthy adolescents and children in RSA.

The purpose of MET55 will be to support licensing of MenACYW conjugate vaccine in India and RSA.

This study will be conducted to evaluate and/or describe the immunogenicity and describe the safety of MenACYW conjugate vaccine in children, adolescents, and adults. The primary aim of the study is to compare the immunogenicity responses obtained after MenACYW conjugate vaccine administration to the responses obtained after the administration of a licensed meningococcal vaccine, Menactra® in children and adolescents. This study will also generate descriptive immunogenicity data from the adult population (18 years of age and above) for MenACYW conjugate vaccine. The safety of the MenACYW conjugate vaccine will be described in the whole study population. Since MenACYW conjugate vaccine has been evaluated in children, adolescents, and adults in many countries without raising any safety concerns, safety assessments will be done up to 30 days after vaccination.

The study has different cohorts according to age and different comparators according to their licensure status in India; hence the study has a modified double-blind design. Only the pharmacist / vaccination study staff in charge of handling the study product will be aware of the type of product administered, whereas the physician and other study staff will remain blinded to the subjects' group allocations throughout the study until the final clinical study report is available. Since the primary objective of this study has a serological endpoint, the laboratory technicians will also remain blinded to the subjects' group allocations throughout the study up to the database lock to avoid any bias.

For ages 2 to 55 years, Menactra® has been chosen as a comparator as it is the licensed meningococcal conjugate vaccine in this age group in India. For ages 56 years and above, Quadri Meningo™ has been chosen as a comparator as this is a vaccine licensed and currently available in the market in India for this age group. However, any locally available licensed meningococcal vaccine will be used as comparator in case Quadri Meningo™ is not available in the Indian market at the time of the study.

MET55 will use a step-wise enrollment only in India. The older populations (adults; ie, Cohorts Ia and Ib) will be recruited before initiating the study in children and adolescents younger than 17 years of age (ie, Cohort II).

A DSMB will be used in this study. The DSMB will be involved in reviewing any life-threatening or fatal SAE cases considered as being related to vaccine throughout the trial. Additionally, the

trial will be monitored by the DSMB, as they will be the only group with access to the unblinded data for the early safety data review (ESDR) that will take place prior to enrolling Cohort II in India. The DSMB will review the unblinded data and advise to either continue the trial as planned or to stop the trial. The procedures governing the function of the DSMB are outlined in the DSMB charter.

3.2 Trial Plan

Approximately 866 healthy adults, adolescents, and children will be assigned into 1 of 3 cohorts and randomized 1:1 to the following groups within those cohorts in India:

Cohort Ia (Adults aged 18 to 55 years; 1 vaccination):

Group 1 (MenACYW conjugate vaccine)

Group 2 (Menactra®)

Cohort Ib (Adults aged ≥ 56 years; 1 vaccination):

Group 3 (MenACYW conjugate vaccine)

Group 4 (Quadri Meningo™ or any locally available licensed meningococcal vaccine)

Cohort II (Children and Adolescents aged 2 to 17 years; 1 vaccination):

Group 5 (MenACYW conjugate vaccine)

Group 6 (Menactra®)

Approximately 466 healthy adolescents and children aged 2 to 17 years will be randomized 1:1 to the following groups in RSA:

Group 7 (MenACYW conjugate vaccine)

Group 8: (Menactra®)

The recruitment in ages 2 to 17 years will be stratified to ensure an equal distribution into 2 subgroups (2 to 9 years and 10 to 17 years) in both of the countries. This will be done to ensure distribution of subjects across the complete age range.

As an expectation of the regulatory agencies in India, it is proposed that this trial will only use a step-wise approach for enrollment in India. Enrollment of Cohorts Ia (adults 18 to 55 years of age) and Ib (adults 56 years of age and older) will take place simultaneously. Enrollment of Cohort II will be initiated once the safety data collected from Day (D) 0 to D07 post-vaccination in a subset of first 100 subjects in adult cohorts Ia and Ib (approximately first 10 subjects from each of the 15 sites across both cohorts) have been reviewed. This ESDR to assess whether proceeding to the younger age cohort (children and adolescents) in India is appropriate, will first be done by the Sponsor's Safety Management Team (SMT) and subsequently by an independent Data Safety Monitoring Board (DSMB) that will be established for independent safety oversight of this study. RSA will not use a step-wise approach to enrollment and will enroll children and adolescents independent of India's ESDR design.

The safety of the investigational product will also be continuously monitored by the Sponsor throughout the study. Periodic safety data review will be performed by the Sponsor's SMT. For

all safety reviews, blinded safety data will be provided to the Sponsor's SMT. A formal additional DSMB review is also proposed following completion of the study.

All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and 30 to 44 days post-vaccination. For subjects in Groups 7 and 8 (ie, RSA only), Human Immunodeficiency Virus (HIV) testing will additionally be performed at baseline if the consent is received.

Safety data will be collected as follows: Immediate unsolicited systemic AEs will be collected within 30 minutes after vaccination. Solicited AE information will be collected from D0 to D07 after vaccination; unsolicited AE information will be collected from D0 to Visit (V) 02 after vaccination, and SAE information (including adverse events of special interest [AESIs]) will be collected throughout the study.

Study Procedures

Table 3.1: Study Procedures 1:
Groups 1 and 2 - Adults 18 to 55 years of age;
Groups 3 and 4 - Adults >= 56 Years of age
Phase III Trial, 3 Visits, 1 Vaccination, 2 Blood Samples, 1 Contact, 30 Days Duration per Subject

Visit (V) / Contact	V01	Contact*	V01-D08 (Home or OPDV)	V02
Trial timelines (day [D])	D0	D03	D08	D30
Time windows (days)	--	+2 days	+2 days	+14 days
Informed consent form signed and dated (*For India: additional consent for A/V recording obtained*)	X			
Inclusion/exclusion criteria	X			
Collection of demographic data	X			
Urine pregnancy test (if applicable)	X			
Medical history	X			
Physical examination†	X			
Review of temporary contraindications for blood sampling‡				X
Contact interactive response technology (IRT) for randomization/dose number assignment/allocation of subject number	X			
Blood sampling (BL), 6 mL§	BL0001			BL0002
Vaccination**	**X**			
Immediate surveillance (30 minutes)	X			
Diary card provided	X			
Contact		X††		
Recording of solicited injection site & systemic reactions	D0 to D07			
Recording of unsolicited AEs	D0 to D30 after vaccination			
Reporting of SAEs (including AESIs)	To be reported throughout the study period			
Diary card reviewed and collected			X‡‡	X
Collection of reportable concomitant medications	X		X	X
Termination of trial				X

*Contact can be a telephone call, visit, or Outpatient Department Visit (OPDV) for India.
†Temperature needs to be measured and recorded in source documents.
‡Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.
§Blood sample at V01 will be drawn before administration of vaccine.
**Subjects will receive 1 dose of MenACYW conjugate vaccine or Quadri Meningo™ (or any locally available licensed meningococcal vaccine for the age) or Menactra®.
††This contact is made 3 to 5 days after the vaccination at V01. If D03 (+2 days) falls on a weekend or holiday, the contact may be made on the following business day. During this contact, the staff will find out whether the subject experienced any SAE (including AESIs) not yet reported, and will remind the subject to continue capturing the safety information in the diary card up to V02, to bring the diary card to the study center at V02, and confirm the date and time of V02.
‡‡Safety data for D0 to D07 after vaccination will be reviewed and collected.

Table 3.2: Study Procedures 2:
Groups 5, 6, 7, and 8 – Children and Adolescents 2 to 17 years of age

Phase III Trial, 2 or 3 Visits, 1 Vaccination, 2 Blood Samples, 1 Contact, 30 Days Duration per Subject

Visit (V) / Contact	V01	Contact*	V02
Trial timelines (days)	D0	D08	D30
Time windows (days)	--	+2 days	+14 days
Informed consent form/Assent form signed and dated (*For India: additional consent for A/V recording obtained; for Republic of South Africa: additional consent for HIV testing obtained*)†	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Urine pregnancy test (if applicable)	X		
Medical history	X		
Physical examination‡	X		
Review of temporary contraindications for blood sampling§			X
Contact interactive response technology (IRT) for randomization/allocation of subject number	X		
Blood sampling (BL) 6 mL**	BL0001		BL0002
Human Immunodeficiency Virus (HIV) test (for subjects in Groups 7 and 8 only)†	X		
Vaccination††	**X**		
Immediate surveillance (30 minutes)	X		
Diary card provided	X		
Contact		X‡‡	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited adverse events (AEs)	D0 to D30 after vaccination		
Reporting of serious adverse events (SAEs, including adverse events of special interest [AESIs])	To be reported throughout the study period		
Diary card reviewed and collected			X
Collection of reportable concomitant medications	X		X
Termination of trial			X

*Contact can be a telephone call, visit, or Outpatient Department Visit (OPDV) for India.
†If all other conditions and inclusion / exclusion criteria are met, then absence of the results of HIV testing will not prevent the randomization and vaccination of the subject. For subjects who had HIV testing prior to the enrollment visit (V01), the Investigator may decide to repeat the test if necessary at V01. The HIV testing will be performed at the study center using local accepted diagnostic test for HIV.

‡Temperature needs to be measured and recorded in source documents.
§Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.
**Blood sample at V01 will be drawn before administration of vaccine.
††Subjects will receive 1 dose of MenACYW conjugate vaccine or Menactra®. Children and adolescents (Cohort II) will not be vaccinated until after the favorable review of the safety data from adults in Cohorts Ia and Ib in India only.
‡‡This contact is made 8 to 10 days after the vaccination at V01. If D08 (+2 days) falls on a weekend or holiday, the contact may

be made on the following business day. During this contact, the staff will find out whether the subject experienced any SAE (including AESIs) not yet reported, and will remind the subject / subject's parent / legally acceptable representative (LAR) to continue capturing the safety information in the diary card up to V02, to bring the diary card to the study center at V02, and confirm the date and time of V02.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Immunogenicity

4.1.1.1 Immunogenicity Endpoints

The primary endpoint for the evaluation of immunogenicity is:

hSBA antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at D30 (+14 days) after vaccination in adolescents and children aged 2 to 17 years in India and RSA ([Group 5 + Group 7] versus [Group 6 + Group 8])

4.1.1.2 Immunogenicity Assessment Methods

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 was 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.

The hSBA testing will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

Testing will be performed on all BL0001 and BL0002 samples from subjects in all groups.

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Immunogenicity

4.2.1.1 Immunogenicity Endpoints

The secondary endpoints for the evaluation of immunogenicity are:

1) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and serum bactericidal assay using baby rabbit complement (rSBA) (in a subset)[a] before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in adults aged 18 to 55 years in India (Group 1 versus Group 2)
2) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[a] before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years in India (Group 3 versus Group 4)
3) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[a] before and at D30 (+ 14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India and RSA ([Group 5 + Group 7] versus [Group 6 + Group 8])
4) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[a] before and at D30 (+ 14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India (Group 5 versus Group 6)
5) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[a] before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in RSA (Group 7 versus Group 8)

4.2.1.2 Immunogenicity Assessment Methods

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

The immunogenicity hSBA assessment method of the meningococcal serogroups A, C, Y, and W antibody titers for the secondary endpoints is the same as that presented in Section 4.1.1.2.

Antibodies to meningococcal antigens (rSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in an SBA utilizing baby rabbit complement. Two-fold dilutions of test sera are prepared in sterile

[a] rSBA data will be generated in a subset of subjects as follows:
- Groups 1, 2, 3, and 4: 50 subjects each
- Groups 5, 6, 7 and 8: 100 subjects each

96-well microtiter plates. Serogroup-specific meningococcal bacteria along with baby rabbit complement are added to the serum dilutions and allowed to incubate. After this incubation period, 10 microliters (µL) of the serum / complement / bacteria mixture is removed and added to a blood agar plate using the tilt method, and then incubated overnight at 37°C with 5% CO_2. Bacterial colonies present on the blood agar plate are then counted. The bactericidal titer of each sample is expressed as the final reciprocal dilution yielding ≥ 50% killing as compared to the T60 (average number of bacteria in each control well after incubation) colony-forming unit (CFU). To report a titer greater than 1:4, clear bactericidal activity must be noted and the next dilution must have a CFU count less than the calculated 20% T60. The LLOQ of the rSBA assay is a titer of 1:4.

This method will be performed on a subset of BL0001 and BL0002 samples corresponding to 50 subjects in each of the following groups: Group 1, Group 2, Group 3, and Group 4; and 100 subjects in each of the following groups: Group 5, Group 6, Group 7, and Group 8, respectively (600 subjects total).

The rSBA testing will be performed at Public Health England, Manchester, United Kingdom.

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

4.3 Observational Endpoints and Assessment Methods

4.3.1 Immunogenicity

4.3.1.1 Immunogenicity Endpoint

The observational endpoints for the evaluation of immunogenicity are:

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[b] before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years by age groups (2 to 9 years of age and 10 to 17 years of age)

4.3.1.2 Immunogenicity Assessment Methods

The immunogenicity hSBA assessment method of the meningococcal serogroups A, C, Y, and W antibody titers for the observational endpoints is the same as that presented in Section 4.1.1.2.

The hSBA testing will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

The immunogenicity rSBA assessment method of the meningococcal serogroups A, C, Y, and W antibody titers for the observational endpoints is the same as that presented in Section 4.2.1.2.

The rSBA testing will be performed at Public Health England, Manchester, United Kingdom.

[b] rSBA data will be generated in a subset of subjects as follows:

- Groups 1, 2, 3, and 4: 50 subjects each
- Groups 5, 6, 7 and 8: 100 subjects each;

This method will be performed on a subset of BL0001 and BL0002 samples corresponding to 50 subjects in each of the following groups: Group 1, Group 2, Group 3, and Group 4; and 100 subjects in each of the following groups: Group 5, Group 6, Group 7, and Group 8, respectively (600 subjects total).

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

4.3.2 Safety

4.3.2.1 Safety Definitions

The following definitions are taken from the 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[c]
- Requires inpatient hospitalization or prolongation of existing hospitalization[d]
- Results in persistent or significant disability / incapacity[e]
- 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 (AR):

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reaction (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" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (eg, injection site pain or headache occurring between D0 and D07 post-vaccination).

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

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[c] 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.

[d] 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.

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

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

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 headache between D0 and D07 is a solicited reaction (i.e., pre-listed in the protocol and CRB), then a headache starting on D07 is a solicited reaction, whereas headache 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 headache, 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.

4.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) injection site reactions occurring up to D07 after vaccination
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to D07 after vaccination
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to D30 after 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 study

4.3.2.3 Safety Assessment Methods

At V01 and V02, the Investigator or a delegate will ask the subject / parent / LAR 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.

4.3.2.3.1 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.

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

After the first vaccination, parents / legally acceptable representatives 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 / legally acceptable representative in the diary card on the day of each 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 legally acceptable representative 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

Subjects or subjects' parents / LARs will be contacted by telephone 3 days after vaccination to remind them to record all safety information in the diary card.

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, study staff will continue

calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

Table 4.1, 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. Note that Table 4.3 applies to all age groups in the study. The scales used in the assessment of the intensity of standard solicited reactions for this study is not fully aligned with Safety Guidelines of sanofi.

Table 4.1: Solicited injection site reactions: terminology, definitions, and intensity scales for children (aged 2 to 9 years)

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
MedDRA PT	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is 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: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

* For the subjective reaction of pain, parents / LARs 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 injection site reactions: terminology, definitions, and intensity scales for adolescents and adults (aged 10 to >= 56 years)

CRB term (MedDRA LLT)	Injection site pain	Injection site erythema	Injection site swelling
MedDRA PT	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is 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: A type of adverse event 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 adverse event 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 adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

* For the subjective reaction of pain, subjects / parents / LARs 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	Headache	Malaise	Myalgia
MedDRA PT	Pyrexia	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event 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 1: A type of adverse event 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 1: A type of adverse event 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: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of adverse event 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 2: A type of adverse event 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 2: A type of adverse event 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: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

* For all reactions but fever, subjects or parents / LARs 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:

Subjects / parents / LARs 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 axillary. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic thermometers must not be used.

4.3.2.3.3 Unsolicited Adverse Events

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

Information on SAEs will be collected and assessed throughout the study, from the time of vaccination until Day 30 after 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 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 (eg, 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:

[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.

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, Table 4.2, and Table 4.3).

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

- Grade 1: A type of AEs 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 AEs 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 subject.
- Grade 3: A type of AEs 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 Section 4.3.2.3.5.

- Action taken for each AE (e.g., medication)

  The action(s) taken by the subject / parent or LAR 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

- 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

4.3.2.3.4 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.

4.3.2.3.5 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the product administered as ***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

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited injection site and systemic reactions will be derived into daily intensity scales 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.

4.4.1.1.2 Maximum Intensity

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

4.4.1.1.3 Presence

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

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

Subjects with at least one non-missing presence for a specific endpoint will be included in the safety analysis tables. 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 but will be listed separately in separate listings.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3 during the solicited period (D0 to D7) after each vaccination.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence during the solicited period (D0 to D7) after each vaccination.

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

4.4.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the solicited period (D0 to D7) considered is derived from the daily intensities as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity (e.g., Grade 3) may also be derived.

4.4.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence 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:

> (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 is incomplete (contains missing data), the overall number of days of occurrence will be considered as Missing.

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period as described in Section 4.4.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- 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).

4.4.1.2 Unsolicited AEs

4.4.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a None intensity event.

Note: Unsolicited AEs with None intensity for a specific endpoint will not be included in the safety analysis tables but will be included in separate listings.

4.4.1.2.2 Intensity

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

> None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

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 protocol 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.

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.

4.4.1.2.3 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" is used to determine the last vaccination before the unsolicited AE.

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE provided in the clinical database and the date of last vaccination as described in Section 4.4.1.2.3:

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

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 0 and 30 days after each vaccination or missing onset date. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the Section 4.4.1.2.3), 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 onset higher than defined above (e.g, >30 days after each vaccination for non-serious AE) will not be included in analysis, but will be listed separately.

4.4.1.2.5 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 is considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

4.4.1.2.6 Serious Adverse Events

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

SAEs 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)

4.4.1.2.7 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF. 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 AESIs occurred during the study)

4.4.1.3 Other Safety Endpoints

4.4.1.3.1 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.4.1.3.2 Action Taken

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

4.4.1.3.3 Seriousness

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

4.4.1.3.4 Outcome

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

4.4.1.3.5 Causality Relationship

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

4.4.1.3.6 Adverse Events 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 subject's status?" has "Adverse Event" checked.
- Safety overview table: A subject 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.

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

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

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

4.4.2.2 hSBA Vaccine Seroprotection

The derived seroprotection indicator for hSBA will be "Yes" if hSBA titer is ≥ 1:8, otherwise seroprotection will be "No". Note: If hSBA titer is missing, the seroprotection for hSBA will be missing.

4.4.2.3 Fold-rise

The derived endpoint of fold-rise is computed as follows for extreme values, to minimize 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

4.4.2.4 hSBA Vaccine Seroresponse

The derived seroresponse for serogroups A, C, Y, and W indicator for hSBA will be "Yes" if

- 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.

4.4.2.5 rSBA Vaccine Seroresponse

The derived seroresponse for serogroups A, C, Y, and W indicator for rSBA will be "Yes" if

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:32.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer

4.4.3 Efficacy

Not applicable

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 year at the time of inclusion.

4.4.4.2 Duration of a Subject in the Trial

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

Maximum (date of last visit, date of termination) – (date of V01 of that subject) +1.

4.4.4.3 Duration of the Study

The duration of study is computed in days as follows:

Maximum of all subjects (date of last visit, date of termination) – Minimum of 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 (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 (seroresponse, ≥ 4-fold rise, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / concentration)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

5.1.1.1 Hypotheses

Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the percentages of subjects who achieve ≥ 1:8 in hSBA titers for meningococcal serogroups A, C, Y,

and W in the combined group (Group 5 + Group 7) are non-inferior to the corresponding percentages in the combined group (Group 6 + Group 8)

Null hypothesis (H0): p(G5 + G7) - p(G6 + 8) ≤ -10%

Alternative hypothesis (H1): p(G5 + G7) - p(G6 + G8) > -10%

where p(G5 + G7) and p(G6 + G8) are the percentages of subjects who achieve ≥ 1:8 in hSBA titers in the combined group (G5 + G7) and the combined groups (G6 +G8), respectively.

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, the CI of the difference in proportions will be computed using the Wilson score method without continuity correction (2). The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

5.1.1.2 Statistical Methods

Each of the serogroups A, C, W, and Y will be tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected. For the 4 non-inferiority hypotheses using the vaccine seroprotection rates, the 95% CI of the difference in proportions between (Group 5 + Group 7) and (Group 6 + Group 8) will be 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

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

5.1.2.2 Statistical Methods

Immunogenicity

Secondary Objectives 1 and 2:

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in adults aged 18 to 55 years (Group 1 versus Group 2) or Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years (Group 3 versus Group 4) in India.

Secondary Objectives 3, 4, and 5:

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in adolescents and children aged 2 to 17 years in India and RSA combined ([Group 5 + Group 7] versus [Group 6 + Group 8]), India only (Group 5 versus Group 6), and RSA only (Group 7 versus Group 8).

In general, categorical variables in Cohorts Ia and Ib (in India), II (in India and RSA) will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) (1) for percentages.

Descriptive analyses on A, C, Y, and W serogroups on D0 and D30 (+14 days) using hSBA and rSBA (in a subset)[b] will be generated as follows:

Descriptive analyses of hSBA include but will not be limited to:

- Geometric mean titers (GMTs) and 95% CI
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI

[b] Note: rSBA data will be generated in a subset of subjects as follows:
- Groups 1, 2, 3, and 4: 50 subjects each
- Groups 5, 6, 7, and 8: 100 subjects each

1

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

Descriptive analyses of rSBA (in a subset) will include but not be limited to:

- GMTs and 95% CI in a subset of age groups
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with rSBA vaccine seroresponse[d] and 95% CI in a subset of age groups

5.1.3 Statistical Methods for Observational Objective(s)

5.1.3.1 Hypothesis

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

5.1.3.2 Statistical Methods

5.1.3.2.1 Immunogenicity

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in children and adolescents aged 2 to 17 years and another set of descriptive statistics on the same children and adolescents by age groups 2 to 9 years and 10 to 17 years in India and RSA combined and separated by each country as well.

In general, categorical variables for the full group in Cohort II and by age groups (2 to 9 years and 10 to 17 years) will be summarized and presented by frequency counts, percentages, and CIs in India and RSA combined ([Group 5 + Group 7]) versus [Group 6 + Group 8]), India only (Group 5 versus Group 6), and RSA only (Group 7 versus Group 8). The 95% CIs of point estimates will

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

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

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

- a post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or
- a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8.

be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) (1) for percentages.

Descriptive analyses on A, C, Y, and W serogroups on D0 and D30 (+14 days) using hSBA and rSBA (in a subset) will be generated as follows:

Descriptive analyses of hSBA includes but will not be limited to:

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

Descriptive analyses of rSBA (in a subset) will be included but not be limited to:

- GMTs and 95% CI in a subset of age groups
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with rSBA vaccine seroresponse and 95% CI in a subset of age groups

5.1.3.2.2 Safety

The Safety Analysis Set (SafAS) is defined as those subjects who have received at least 1 dose of the study vaccine and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

Safety analyses 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 vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken
- Immediate unsolicited systemic AEs within 30 minutes and unsolicited AEs occurring up to D30 after vaccination will be summarized
- The number and percentage of subjects reporting any unsolicited 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 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 study
- Exact (Clopper-Pearson) (1) 2-sided 95% CIs will be calculated for the percentages

For exploratory purpose, main safety and immunogenicity parameters may be presented according to baseline HIV status in Groups 7 and 8.

5.1.4 Complementary Output

5.1.4.1 Subgroup Analysis

Subgroup analyses by gender, race (only if more than 5% of subjects had different race) and HIV status at baseline (only if more than 5% of subjects had different HIV status) for the RSA subjects will be provided in Appendix 15 of the CSR.

The gender subgroup analyses will have two categories (Female and Male), the race subgroup analyses will have four categories (White, Black or African American, Asian, and Other), and the HIV status at baseline subgroup analyses for the RSA subjects will have three categories (Positive, Negative and Unknown).

For primary and secondary immune endpoints after meningococcal vaccinations, subgroup analyses by gender, race will be conducted for all groups as well as groups combined by countries at D0 and 30 days after meningococcal vaccination. Subgroup analyses by HIV status at baseline will be conducted only for the RSA subjects at D0 and 30 days after meningococcal vaccination.

For safety responses, these subgroup analyses will be performed in all groups as well as groups combined by countries after meningococcal vaccination.

Immunogenicity analyses:

The subgroup analyses in immunogenicity will be performed based on PPAS.

- Percentage of subjects with hSBA antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W assessed at D30 (+14 days) after vaccination in adolescents and children aged 2 to 17 years in India and RSA ([Group 5 + Group 7] and [Group 6 + Group 8]) – Per-Protocol Analysis Set
- hSBA GMTs and 95% CI – Per-Protocol Analysis Set
- Percentage of subjects with hSBA titer≥ 1:8 and 95% CI – Per-Protocol Analysis Set
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA and 95% CI – Per-Protocol Analysis Set
- rSBA GMTs and 95% CI – Per-Protocol Analysis Set
- Percentage of subjects with rSBA titer ≥ 1:128 and 95% CI – Per-Protocol Analysis Set
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by rSBA and 95% CI – Per-Protocol Analysis Set

Safety analyses:

Safety overview after vaccination – Safety Analysis Set

5.1.4.2 Sensitivity Analysis due to the COVID-19 pandemic

As this study was conducted during Coronavirus Disease 2019 (COVID-19) pandemic, the impact of COVID-19 pandemic situation on study conduct will be summarized through impact on visit procedures, study completion and major/critical protocol deviations due to COVID-19. The subset of subjects who were impacted by COVID-19 is 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 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 outputs will be provided in Appendix 15 of the CSR.

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

- 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 by COVID-19
- To summarize baseline demographics for subjects impacted / non-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

Immunogenicity analyses

The sensitivity analyses in immunogenicity will be performed based on PPAS and FAS.

The primary endpoint for immunogenicity will be assessed:

- Percentage of subjects with hSBA antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at D30 (+14 days) after vaccination in adolescents and children aged 2 to 17 years in India and RSA ([Group 5 + Group 7] and [Group 6 + Group 8])

Safety analyses

Safety overview after vaccine injection –Safety Analysis Set

5.1.4.3 Sensitivity Analysis due to Blood Sample Issues

If applicable and necessary, additional immunogenicity sensitivity analyses will be performed for subjects with blood samples handled incorrectly during collection, processing, storage or shipment, and may have potential impact on the analysis results (eg, blood samples stored out of temperature after a power outage) based on the PPAS. The outputs will be provided in Appendix 15 of the CSR.

The endpoint for the sensitive analyses will be the GMT.

- hSBA GMTs and 95% CI at each time point for each group by blood sample status – Per-Protocol Analysis Set

5.2 Analysis Sets

Three types of analysis sets will be used: the Full Analysis Set (FAS), the Per-Protocol Analysis Set (PPAS), and the Safety Analysis Set (SafAS).

5.2.1 Full Analysis Set

The FAS is defined as the subset of randomized subjects who received at least 1 dose of the study vaccine and had a valid post-vaccination blood sample result.

5.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received at least 1 dose of the study vaccine[e] and have any safety data available.

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

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

5.2.3 Per-Protocol Analysis Set

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive the vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of the vaccine was not done as per-protocol
- Subject did not receive the vaccine in the proper time window

[e] or which safety data are scheduled to be collected

- Subject did not provide the post-dose serology sample at Visit 2 in the proper time window or a post-dose serology sample was not drawn
- 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.

In addition to the reasons listed above, subjects will also be excluded from the PPAS if their Visit 2 serology sample did not produce a valid test result (ie, results for all antigens are missing).

In the event of a local or national immunization program with oral poliovirus vaccine (OPV), subjects who receive 1 or more doses of OPV at any time during the study will not be withdrawn from the study. Every effort should be made to keep a gap of at least 2 weeks between OPV and MenACYW conjugate vaccines, if possible.

Other Analysis Set(s)

Enrolled / Screened subjects

As this study has no screening visit, enrolled subjects are subjects for whom signed off the inform consent form (ICF) and a CRF has been created.

Randomized subjects

A randomized subject is an enrolled subject for whom an injection group has been allocated and with any available data in CRF.

5.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS analysis set and a supplemental analysis based on FAS will be performed to evaluate consistency of the results, If the difference between PPAS and FAS is greater than 10%. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

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

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

Generally, no replacement will be done for safety missing data and outliers. 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.

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

5.3.1.4 Start Date and End 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 according to the last vaccination (computed according to the Section 4.4.1.2.3). 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.

The computational rule for undetectable responses < LLOQ and ≥ ULOQ is described in Section 4.4.2.1.

5.3.3 Efficacy

Not applicable.

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

Calculation of Sample Size:

Approximately 1332 subjects will be enrolled. An estimated 15% drop-out rate (only ages 2 – 17 years) from enrollment will result in approximately 1190 subjects in the per-protocol population available for immunogenicity analyses.

For the Primary Objective

With 396 evaluable subjects in the combined group (Gr5 + Gr7) and 396 evaluable subjects in the combined group (Gr6 + Gr8), the study will have 90% power using Farrington and Manning's method to declare the non-inferiority of the combined group (Gr5+ Gr7) versus the combined group (Gr6 + Gr8) based on A, C, Y, W antibodies in adolescents and children aged 2 to 17 years (assuming 15% drop-out rate for each group). The power is calculated with the assumption that the estimate from the investigational group equals that of the control group.

Table 5.2: Power of the study based on the primary objective of non-inferiority in children and adolescents aged 2 to 17 years

Antigen	Estimated* MenACYW	Estimated Menactra®	Non-inferiority	Power
A	76%	76%	10%	91%
C	94.5%	94.5%	10%	> 99.9%
Y	89%	89%	10%	> 99.9%
W	95%	95%	10%	> 99.2%
Overall				90%

Note: Evaluable subjects:
Combined group (Gr5 + Gr7) = 396 subjects
Combined group (Gr6 + Gr8) = 396 subjects

Since the hypothesis needs to be met for all serogroups, no alpha adjustment for multiple comparisons is necessary in these calculations.

* Estimated seroresponses are based on the results of a study (3) conducted in India in subjects aged 2 to 75 years. The estimates were the average of overall rates of 2 age groups (2 to 10 years and 11 to 18 years). Borrow et al. reported that incidence rates vary in RSA by province but are currently low overall (0.36/100 000 in 2014) with the majority of disease caused by MenW, followed by MenB. Approximately 66-77% of disease is caused by MenA, C, Y, or W. Due to any lack of published data from RSA it is assumed that the response in subjects aged 2-17 years will be similar between India and RSA. Additionally, any variability should balance itself out due to the wider age range.

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.

Besides, 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 Trial or Planned Analyses

In protocol, the planned analysis the primary immunogenicity analyses will be performed on the PPAS analysis set and will be confirmed on the FAS. In SAP, we change that all immunogenicity analyses will be performed on the PPAS analysis set and a supplemental analysis based on FAS will be performed to evaluate consistency of the results, If the difference between PPAS and FAS is greater than 10%. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

For safety analyses, will include the number and percentage of subjects reporting any unsolicited AEs will be summarized, not only non-serious AEs. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

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.

3 Lalwani S, Agarkhedkar S, Gogtay N, et al. Safety and immunogenicity of an investigational meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy Indian subjects aged 2 to 75 years. Int J Infect Dis. 2015;38:36-42.

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