NCT04084769

Immunogenicity and Safety of a Booster Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults

Phase IIIb, open-label (the laboratory technicians will be blinded to group assignment), partially randomized, parallel-group, active-controlled, multi-center study to evaluate the antibody persistence 3-6 years after the priming vaccination with MenACYW conjugate vaccine or the licensed vaccine Menveo®, and to evaluate the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine when given alone or concomitantly with the first dose of licensed Meningococcal serogroup B vaccines in adolescents and adults in the United States and Puerto Rico

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET59
Development Phase:	Phase IIIb
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, Pennsylvania (PA) 18370-0187, USA
Investigational Product(s):	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid Solution / Intramuscular (IM)
Indication For This Study:	MenACYW conjugate vaccine as a booster dose in adolescents and adults when given alone or concomitantly with the first dose of licensed Meningococcal serogroup B vaccines
Version and Date of the SAP Core Body Part:	Version 3.0, 13 OCT, 2020

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List of Abbreviations

µL	microliters
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CFU	colony-forming unit
CI	confidence interval
CO_2	carbon dioxide
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CSR	Clinical Study Report
D	day
EDC	electronic data capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCI	Global Clinical Immunology
GMT	geometric mean titer
GMTR	geometric mean titer ratio
hSBA	serum bactericidal assay using human complement
ICF	informed consent form
ICH	International Council for Harmonization
IMD	invasive meningococcal disease
IME	important medical event
IMP	investigational medicinal product
IRT	interactive response technology
LLOQ	lower limit of quantification
LLT	lowest level term
MA	memory aid
MAAE	medically-attended adverse event
MCV4	quadrivalent meningococcal conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MenB	meningococcal serogroup B
mL	milliliter
non-IMP	non-investigational medicinal product
NM	non-measurable

PPAS	Per-Protocol Analysis Set
PS	polysaccharides
PT	preferred term
RCDC	Reverse Cumulative Distribution Curve
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SAP	statistical analysis plan
SafAS	safety analysis set
SBA	serum bactericidal assay
SOC	system organ class
ULOQ	upper limit of quantification
US	United States

1 Introduction

This trial will evaluate the antibody persistence, 3-6 years after the priming vaccination with quadrivalent Meningococcal Polysaccharide (serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) or the licensed vaccine Menveo®, and will evaluate the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine when given alone or concomitantly with the first dose of licensed meningococcal serogroup B (MenB) vaccines in adolescents and adults in the United States (US) and Puerto Rico.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis (N meningitidis)*, a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). At least 12 distinct meningococcal groups have been classified based on the immunochemistry of the capsular polysaccharides (PS). Some strains are more likely than others to cause infection (1) (2) (3). 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 age group. The highest incidence rate in Europe is caused by serogroup B, followed by serogroup C (5). In the US, the incidence rate of IMD in 2013 was 0.14 per 100 000 in all age groups, 0.83 per 100 000 in infants less than 1 year of age, 0.62 per 100 000 in toddlers 1 year of age, 0.27 per 100 000 in toddlers and children 2 to 4 years of age, and 0.02 per 100 000 in children and adolescents 5 to 17 years of age. The age specific incidence rate in 2013 was 0.08 per 100 000 in 50 to 64 years of age, 0.03 per 100 000 in 65 to 74 years of age, 0.14 per 100 000 in 75 to 84 years of age, and 0.43 per 100 000 in 85 years of age and older (6).

The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, Y, and W in all target age groups.

The current MenACYW conjugate vaccine formulation was selected based on data provided by 2 studies (MET28 [Phase I] and MET32 [Phase I/II]). Subsequently, it was studied in 4 Phase II studies, which included infants/toddlers (MET39), toddlers (MET54), adolescents (MET50), and adults 56 years of age and older (MET44). MET39, MET44, MET50 were conducted in the US, and MET54 was conducted in Finland.

The MenACYW conjugate vaccine has also been evaluated in 6 completed Phase III studies, which included toddlers (MET51, MET57), children (MET35), adolescents and adults 10 to 55 years of age (MET43), adolescents and adults 15 years of age and older (MET56), and adults 56 years of age and older (MET49). MET35, MET43, MET49, and MET56 were conducted in the US; MET51 was conducted in European Union (EU) region (Spain, Germany, Hungary, and Finland); and MET57 was conducted in Thailand, South Korea, Russia, and Mexico.

MET56 was a study to compare the immunogenicity and describe the safety of a booster dose of MenACYW conjugate vaccine compared to Menactra vaccine in quadrivalent meningococcal conjugate vaccine (MCV4)-primed (ie, the Menactra vaccine-primed or Menveo vaccine-primed) adolescents and adults in the US. This study will explore the safety and immunogenicity of the antigens contained in the MenACYW conjugate vaccine following a booster dose of the MenACYW conjugate vaccine administered concomitantly with the first dose of the licensed MenB vaccines (Trumenba vaccine and Bexsero vaccine) in adolescents and adults who received the first vaccination with an MCV4 (ie, the MenACYW conjugate vaccine or Menveo vaccine), 3-6 years earlier. Subjects will complete the rest of the vaccinations required from the approved schedules for the MenB vaccines, but outside of the objectives of this study (ie, the Sponsor will be responsible for reimbursing the sites for the cost of the additional MenB vaccine doses; however, no safety or immunogenicity information will be collected).

2 Trial Objectives

2.1 Primary Objectives

1. To demonstrate the vaccine seroresponse sufficiency of meningococcal serogroups A, C, Y, and W following the administration of a booster dose of MenACYW conjugate vaccine in Group 1 subjects who were first vaccinated with 1 dose of MenACYW conjugate vaccine 3-6 years before the booster dose
2. To demonstrate the vaccine seroresponse sufficiency of meningococcal serogroups A, C, Y, and W following the administration of a booster dose of MenACYW conjugate vaccine in Group 2 subjects who were first vaccinated with 1 dose of Menveo vaccine 3-6 years before the booster dose

The endpoints for the primary objectives are presented in Section 4.1.1.1.

2.2 Secondary Objectives

Immunogenicity

1) To describe the vaccine seroresponse, seroprotection (serum bactericidal assay using human complement [hSBA] titer ≥ 1:8), and antibody responses (geometric mean titers [GMTs]) of meningococcal serogroups A, C, Y, and W measured using hSBA in serum specimens collected 6 days (± 1 day) after vaccination in a subset of 50 subjects per group (Groups 1 and 2)
2) To describe the vaccine seroresponse, seroprotection (hSBA titer ≥ 1:8), and antibody responses (GMTs) to serogroups A, C, Y, and W measured using hSBA on day (D)0 (pre-vaccination) and D30 (+ 14 days) after vaccination with MenACYW conjugate vaccine alone (Groups 1 and 2)
3) To describe the antibody persistence (GMTs and vaccine seroprotection; hSBA titer ≥ 1:8) of meningococcal serogroups A, C, Y, and W before a booster dose in subjects who received either MenACYW conjugate vaccine or Menveo vaccine 3-6 years earlier

4) To describe the antibody persistence (GMTs and vaccine seroprotection; hSBA titer ≥ 1:8) of meningococcal serogroups A, C, Y, and W in subjects who received either a single dose MenACYW conjugate vaccine (subjects randomized to MET59 Groups 1, 3, and 4) or Menveo vaccine (subjects assigned to MET59 Group 2), as part of study MET50, or MET43 (subjects randomized to MET59 Groups 1, 3, and 4)

5) To describe the vaccine seroresponse, seroprotection (hSBA titer ≥ 1:8), and antibody responses (GMTs) to the antigens present in MenACYW conjugate vaccine, when MenACYW conjugate vaccine is given concomitantly with MenB vaccine (Groups 3 and 4), compared to those when it is given alone (Group 1)

The endpoints for the secondary objectives are presented in Section 4.2.1.1.

2.3 Observational Objectives

Immunogenicity

1) To describe the kinetics of antibody titers against meningococcal serogroups (A, C, Y, and W) measured by hSBA assessed at D0, D06 (only for Groups 1 and 2), D30 after vaccination with MenACYW conjugate vaccine when it is administered alone or concomitantly with MenB vaccines, and also at baseline and D30 in subjects after having received a single dose of either MenACYW conjugate vaccine (subjects randomized to MET59 Groups 1, 3, and 4) or Menveo vaccine (subjects assigned to MET59 Group 2), as part of study MET50, or MET43 (subjects randomized to MET59 Groups 1, 3, and 4)

2) To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+ 14 days) after vaccination with MenACYW conjugate vaccine measured by serum bactericidal assay using baby rabbit complement (rSBA) in a subset of 50 subjects per group (Groups 1 and 2)

Safety

To describe the safety profile of a booster dose of MenACYW conjugate vaccine, when given alone or when given concomitantly with a MenB vaccine.

The endpoints for the observational objective are presented in Section 4.3.1.1.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

The MET59 study is a Phase IIIb, open-label (the laboratory technicians will be blinded to group assignment), partially randomized, parallel-group, active-controlled, multi-center study to evaluate the antibody persistence 3-6 years after the priming vaccination with either MenACYW conjugate vaccine or the licensed Menveo vaccine, and to evaluate the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine when administered alone or concomitantly with licensed MenB vaccines in adolescents and adults in the US and Puerto Rico.

A total of 600 subjects who were vaccinated 3-6 years earlier in study MET50 are planned to be enrolled. Approximately 400 healthy adolescents and adults who had received 1 dose of either MenACYW conjugate vaccine (Group 1, N=200) or Menveo vaccine (Group 2, N=200) as part of the MET50 study will receive a booster vaccination with MenACYW conjugate vaccine. Approximately 200 healthy adolescents and adults who had received 1 dose of MenACYW conjugate vaccine will receive a booster vaccination with MenACYW conjugate vaccine administered concomitantly with a MenB vaccine (Group 3, MenACYW conjugate vaccine + Trumenba vaccine, N=100; and Group 4, MenACYW conjugate vaccine + Bexsero vaccine, N=100). If needed to meet enrollment requirements, MenACYW conjugate vaccine-primed subjects from the MET43 study could also be considered as source of subjects to be enrolled in Group 1, 3, or 4. Additionally, the population of Menveo vaccine-primed subjects could be enriched with individuals who received 1 dose of Menveo vaccine 3-6 years prior to enrollment in this trial as part of their regular adolescent vaccination schedule and who are 13-25 years of age; ie, non-MET50 subjects).

MenACYW conjugate vaccine-primed subjects (from either MET50 or MET43) will be randomized in a 2:1:1 ratio to receive 1 dose of MenACYW conjugate vaccine alone (Group 1) or to receive 1 dose of MenACYW conjugate vaccine concomitantly with 1 dose of a licensed MenB vaccine (Trumenba vaccine [Group 3] or Bexsero vaccine [Group 4]).

Subjects primed with Menveo vaccine in MET50 or outside of Sanofi Pasteur trials will be assigned to Group 2 (these subjects will not be randomized).

3.2 Trial Plan

Eligible subjects will be identified and recruited. Subjects who are ≥ 13 to < 18 years of age will sign an Assent Form and their parent / guardian will sign and date the Informed Consent Form (ICF) before any procedure or treatment associated with the trial is performed. Subjects who are 18 years of age and older will sign and date the ICF before any procedure or treatment associated with the trial is performed.

Vaccination

MenACYW conjugate vaccine-primed subjects (from either MET50 or MET43) will be randomized in a 2:1:1 ratio to receive 1 dose of MenACYW conjugate vaccine alone (Group 1) or to receive 1 dose of MenACYW conjugate vaccine concomitantly with 1 dose of a licensed MenB vaccine (Trumenba vaccine [Group 3] or Bexsero vaccine [Group 4]). Subjects primed with Menveo vaccine in MET50 or outside of Sanofi Pasteur trials will be assigned to Group 2 (these subjects will not be randomized). Study vaccines will be administered according to the following schedule:

Group 1:	MenACYW conjugate vaccine on D0	(n=200)
Group 2:	MenACYW conjugate vaccine on D0	(n=200)
Group 3:	MenACYW conjugate vaccine + Trumenba vaccine on D0	(n=100)
Group 4:	MenACYW conjugate vaccine + Bexsero vaccine on D0	(n=100)

Note: In order to comply with the US Food and Drug Administration (FDA)-approved schedules for the respective MenB vaccines, subjects in Group 3 and Group 4 may choose to receive the second dose of MenB vaccine at Visit 2 (D30) after all the study procedures have been completed. Subjects in Group 3 should receive a third dose (or second dose if the alternate 2-dose Trumenba vaccine schedule is used instead by the study Investigators) of Trumenba vaccine on D180, which is not a study visit. These vaccinations for completion of the MenB schedules will take place outside of the objectives and scope of this study and thus will not be described in this SAP.

Blood Sampling

All subjects will provide a pre-vaccination (baseline) blood sample on D0 and a post-vaccination blood sample on D30 (+ 14 days) (for subjects in Group 3 and Group 4, the post-vaccination blood sample will be provided prior to receiving a second dose of MenB vaccine on D30). A subset of the first 50 subjects enrolled in Groups 1 and 2 (total of 100 subjects) will provide an additional post-vaccination blood sample on D06 (± 1 day). This subset will have 3 visits in total.

Collection of Safety Data

Safety data will be collected as follows:

- All subjects will be followed for safety from Visit 1 to D180 after the last vaccination.
- All subjects will be observed for 30 minutes after vaccination on D0 and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited systemic AEs in the (electronic) case report book (CRB).
- The subjects or subjects' parent / guardian will record information in a diary card about solicited reactions from D0 to D07 after vaccination on D0 and unsolicited AEs from D0 to D30.
- Serious adverse events (SAEs) (including adverse events of special interest [AESIs]) and medically-attended adverse events (MAAEs) will be recorded throughout the study. The subjects or subjects' parent / guardian will record information in a diary card about possible SAEs and MAAEs from D0 to D30. Information about possible SAEs and MAAEs will also be recorded in a memory aid (MA) from D30 until the 6-month (+ 14 days) follow-up telephone call. The subjects or subjects' parent / guardian will be asked to notify the site immediately about any potential SAE at any time during the study.
- The completed diary cards will each be collected and reviewed with the subjects' parent / guardian at the subsequent visit.
- Staff will contact the subjects' parent / guardian by telephone within 14 days after the vaccination visit (D0) to remind them about the forthcoming study visit. If a subject's participation in the study is discontinued, the information recorded on the diary card will be reviewed at this time and the diary card will be retrieved by the site.
- Staff will contact the subjects or subjects' parent / guardian by telephone 8 days (+ 2 days) after the vaccination visit (D0) to identify the occurrence of any SAEs (including AESIs) and / or MAAEs not yet reported and to remind them to complete the diary card and to bring it back to the next visit.

- Staff will contact the subjects or subjects' parent / guardian by telephone at 6 months (+ 14 days) after vaccination on D0 to review the MA and identify the occurrence of any MAAEs and SAEs (including AESIs) that have not been reported.

The Tables of Study Procedures in given in

Table 3.1 and Table 3.2 below.

Table 3.1: Study procedures – Main Cohort (Excluding the Subset Cohort)

Phase IIIb Study, 2 Visits, 1-2 Vaccinations, 2 Blood Samples, 2 Telephone calls, 180 Days' Duration Per Subject

Visit/Contact	**Visit 1**	**Telephone Call 1**	**Visit 2†**	**Telephone Call 2†**
Study timelines (days)	D0	D08	D30	D180
Time windows (days)		+2 days	+14 days	+14 days
Informed consent form/assent form (if applicable)	X			
Inclusion/exclusion criteria	X			
Collection of demographic data	X			
Urine pregnancy test (if applicable)	X			
Medical history	X			
Physical examination‡	X			
Contact interactive response technology (IRT) system for randomization/allocation of subject number/vaccine group assignment	X			
Review of temporary contraindications for blood sampling§	X		X	
Randomization/allocation of subject number/assignment of blood subset	X			
Blood sampling (BL), 20 mL**	BL0001		BL0002	
Vaccinations	X			
Immediate surveillance (30 minutes)	X			
Diary card provided	X			
Telephone call		X‡‡		X§§
Recording of solicited injection site and systemic reactions	X			
Recording of unsolicited adverse events	D0 to D30			
Diary card collected and reviewed			X	
Reporting of SAE (including AESIs) and MAAEs***	To be reported throughout the study period			
Collection of reportable concomitant medications	X		X	
Collection of serious adverse events	To be reported throughout the study period			
Memory aid provided†††			X	
Termination of active phase of trial			X	
Completion of 6-month follow-up				X

Abbreviations: AESI, adverse event of special interest; BL, blood sampling; D, day; MAAEs, medically-attended adverse events; SAE, serious adverse event
† Subjects in Group 3 and Group 4 may choose to receive the second dose of MenB vaccine at Visit 2 (D30) after all the study procedures have been completed. Subjects in Group 3 should receive a third dose (or second dose if the 2-dose schedule is used instead by the study Investigators) of MenB vaccine on D180, which is not a study visit. These vaccinations for completion of the MenB schedules will take place outside of the objectives of this study and thus will not be described in this protocol.
‡ Temperature needs to be measured and recorded in source document.
§ Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the subsequent blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw. If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.
** A blood sample will be collected prior to vaccination at D0. A blood sample will be collected from all subjects in Group 3 and Group 4 prior to receiving a second dose of MenB vaccine at D30 (given outside of the objectives of the study).
‡‡This call is made 8 days after the vaccination on D0. If Day 8 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported; and the staff will remind the subject or subject's parent/guardian to continue using the diary card and to bring the diary card to the D30 (+14 days) visit; the staff will confirm the date and time of the D30 visit.
§§ Staff will contact the subject or subject's parent/ guardian by telephone at 6 months (180 days + 14 days) after vaccination on D0 to identify the occurrence of any SAEs (including any AESIs) and MAAEs not yet reported.
*** 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. MAAEs that occur between D0 visit and D30 visit and between D30 visit and Telephone Call 2 will be recorded as unsolicited AEs.
†††The memory aid is used only for the recording of SAEs (including AESIs) and MAAEs from D30 visit to the 6-month follow-up phone call (Telephone Call 2)

Table 3.2: Study procedures – Subset Cohort (Subset of 100 Subjects from Groups 1 and 2)

Phase IIIb Study, 3 Visits, 1 Vaccination, 3 Blood Samples, 2 Telephone calls, 180 Days' Duration Per Subject

Visit/Contact	**Visit 1**	**Visit 2**	**Telephone Call 1**	**Visit 3**	**Telephone Call 2**
Study timelines (days)	D0	D06	D08	D30	D180
Time windows (days)		±1 day	+2 days	+14 days	+14 days
Informed consent form/assent form (if applicable)	X				
Inclusion/exclusion criteria	X				
Collection of demographic data	X				
Urine pregnancy test (if applicable)	X				
Medical history	X				
Physical examination‡	X				
Contact interactive response technology (IRT) system for randomization/allocation of subject number/vaccine group assignment	X				
Review of temporary contraindications for blood sampling§	X	X		X	
Randomization/allocation of subject number/assignment of blood subset	X				
Blood sampling (BL), 20 mL**	BL0001	BL0002		BL0003	
Vaccinations††	X				

Visit/Contact	Visit 1	Visit 2	Telephone Call 1	Visit 3	Telephone Call 2
Immediate surveillance (30 minutes)	X				
Diary card provided	X				
Telephone call			X‡‡		X§§
Recording of solicited injection site and systemic reactions	X				
Recording of unsolicited adverse events	D0 to D30				
Diary card collected and reviewed				X	
Reporting of SAE (including AESIs) and MAAEs***	To be reported throughout the study period				
Collection of reportable concomitant medications	X	X		X	
Collection of serious adverse events	To be reported throughout the study period				
Memory aid provided†††				X	
Termination of active phase of trial				X	
Completion of 6-month follow-up					X

Abbreviations: AESI, adverse event of special interest; BL, blood sampling; D, day; MAAEs, medically-attended adverse events; SAE, serious adverse event

‡ Temperature needs to be measured and recorded in source document.

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

** A blood sample will be collected prior to vaccination at D0. A subset of the first 50 subjects enrolled in Groups 1 and 2 (total of 100 subjects) will provide an additional post-vaccination sample on D06 (±1 day).

‡‡This call is made 8 days after the vaccination on D0. If Day 8 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported; and the staff will remind the subject or subject's parent/guardian to continue using the diary card and to bring the diary card to the D30 (+14 days) visit; the staff will confirm the date and time of the D30 visit.

§§ Staff will contact the subject or subject's parent/ guardian by telephone at 6 months (180 days + 14 days) after vaccination on D0 to identify the occurrence of any SAEs (including any AESIs) and MAAEs not yet reported.

*** 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. MAAEs that occur between D0 visit and D30 visit and between D30 visit and TC2 will be recorded as unsolicited AEs.

†††The memory aid is used only for the recording of SAEs (including AESIs) and MAAEs from D30 visit to the 6-month follow-up phone call (Telephone Call 2).

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Immunogenicity

4.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, pre-vaccination) and 30 days (+14 days) after vaccination in Group 1
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, pre-vaccination) and 30 days (+14 days) after vaccination in Group 2

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 is assigned.

Antibodies to Meningococcal Antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in a serum bactericidal assay (SBA) utilizing human complement. 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 in Global Clinical Immunology (GCI), at Sanofi Pasteur, Swiftwater, PA or at a qualified contract laboratory for GCI.

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) Vaccine seroresponse, seroprotection, and GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 6 days post-vaccination in a subset of 50 subjects per group (Groups 1 and 2)
2) Vaccine seroresponse, seroprotection, and GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine alone (Groups 1 and 2)
3) Vaccine seroprotection and GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA at baseline in subjects before receiving a booster dose of MenACYW conjugate vaccine (Groups 1, 2, 3, and 4), 3-6 years after receiving their primary MCV4 vaccination

4) Vaccine seroprotection and GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA at baseline and 30 days after vaccination in subjects after having received a single dose of either MenACYW conjugate vaccine (subjects randomized to MET59 Groups 1, 3, and 4) or Menveo vaccine (subjects assigned to MET59 Group 2), as part of study MET50, or MET43 (subjects randomized to MET59 Groups 1, 3, and 4)
5) Vaccine seroresponse, seroprotection, and GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine when given alone (Group 1) or co-administered with Trumenba vaccine or Bexsero vaccine (Groups 3 and 4)

4.2.1.2 Immunogenicity Assessment Methods

The immunogenicity assessment method for the secondary endpoints for hSBA is the same as that presented in Section 4.1.1.2.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Immunogenicity

4.3.1.1 Immunogenicity Endpoints

The observational endpoints for the evaluation of immunogenicity are:

1) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at D0, D06, and D30 after booster vaccination
2) Antibody titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days (+ 14 days) after vaccination with MenACYW conjugate vaccine in a subset of the first 50 subjects enrolled in Group 1 and Group 2 (total of 100 subjects)

4.3.1.2 Immunogenicity Assessment Methods

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 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[a] (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

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

dilution must have a CFU count less than the calculated 20% T60. The LLOQ of the rSBA assay is a titer of 1:4. The rSBA testing will be performed in Public Health England, Manchester, United Kingdom or at another qualified contract laboratory for GCI. In case of insufficient serum sample, the conduct of 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 International Council for Harmonization (ICH) E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event:

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore, an AE may be:

- A new illness
- The worsening of a pre-existing condition
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include SAEs and non-serious AEs.

Surgical procedures are not AEs; they are the action taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the trial period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing 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 (eg, asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event:

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 adverse reactions (AR).

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility).

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.

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 out-patient treatment with no hospitalization.

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

The assessment of these reactions by the Investigator is mandatory.

Unsolicited Adverse Event / Adverse Reaction:

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 (ie, prelisted 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.

Medically-Attended Adverse Event:

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 telephone 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.

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 Adverse Event:

Systemic AEs are all AEs that are not injection or administration site reactions. Therefore, they include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Adverse Event of Special Interest:

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 (eg, regulators) might also be warranted.

4.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

1) 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 vaccination(s)

2) 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(s)
3) 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(s)
4) 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(s)
5) 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) after vaccination(s) from D0 through the end of the trial
6) Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome for MAAEs from D30 visit to the 6-month follow-up contact. MAAEs will be collected as unsolicited AEs up to the D30 (+ 14 days) visit

4.3.2.3 Safety Assessment Methods

At the D30 visit, the Investigator or a delegate will ask the subjects or the subjects' parent / guardian about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

4.3.2.3.1 Immediate Post-vaccination Observation Period

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination surveillance should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the 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 Vaccinations)

After vaccination, subjects or the subjects' parent / guardian 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 subjects or the subjects' parent / guardian in the diary card on the day of vaccination and for the next 7 days (ie, Day 0 through Day 7) 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 (eg, medication)

  The action(s) taken by the subjects or subjects' parent / 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

Subjects or the subjects' parent / guardian will be contacted by telephone 8 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 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 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 / 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 for adolescents or adults (aged >= 12 years)

CRB term (MedDRA lowest level term [LLT])	**Fever**	**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 / 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:

Subjects or the subjects' parent / guardian 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 trial is oral. Pre-vaccination temperature is also systematically collected by the Investigator in the source document. Tympanic thermometers must not be used.

4.3.2.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, subjects or subjects' parent / guardian will be instructed to record any other medical events that may occur. 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 (electronic) 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 (eg, outcome, medical history, results of investigations, copy of hospitalization reports. See 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

[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.

- Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant
- Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention
- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 4.3.2.7.

- Action taken for each AE (eg, medication)

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

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

For each SAE, the Investigator will complete all seriousness criteria that apply (outcome, elapsed time, and "Relationship to Study Procedures")

- Whether the AE caused study discontinuation

4.3.2.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from inclusion until 6 months after vaccination.

Any SAE occurring at any time during the trial will be reported by the Investigator through the electronic data capture (EDC) system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE is to be reported, either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports. The Investigator will assess the causal relationship between the SAE and the investigational product as either "Not related" or "Related", as described in protocol.

See protocol for further details on SAE reporting.

4.3.2.5 Medically-Attended Adverse Events

MAAE information will be collected throughout the study. MAAEs that occur from D0 to the D30 (+ 14 days) visit will be recorded as unsolicited AEs on the diary card as part of all

unsolicited AEs collected for this post-vaccination period. MAAEs that occur from D30 to D180 (+ 14 days) will be recorded as such in the MA. An MAAE that occurs within the study period but meets the definition of an SAE should be reported only on the SAE Reporting Form, and not on the MAAE page of the CRF.

The Investigator will assess the causal relationship between the MAAE and the investigational or study product as either "Not related" or "Related," as described in Section 4.3.2.6.

4.3.2.6 Adverse Events of Special Interest

The following AEs will be captured as AESIs throughout the study:

- Generalized seizures (febrile and non-febrile) (7) (8)
- Kawasaki disease (9) (10)
- Guillain-Barré syndrome (11)
- Idiopathic thrombocytopenic purpura (12) (13)

These events have been listed as AESIs on the basis of the feedback received from the European Union regulators for other studies (conducted in younger age groups).

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 protocol. Further instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

4.3.2.7 Assessment of Causality

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

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.

Adverse events 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

[a] ICH Guidelines, Clinical Safety Data Management E2A

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 Immunogenicity

4.4.1.1 Computed Values for Analysis

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

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

4.4.1.2 Seroprotection

hSBA vaccine seroprotection for serogroups A, C, Y, and W is defined as hSBA titer ⩾1:8.

4.4.1.3 Fold-Rise

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

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

If the computed value is ≥ 4, then the derived ≥ 4-fold rises indicator will be "Yes" for that test, otherwise ≥ 4-fold rises will be "No".

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

4.4.1.4 A, C, Y, W Seroresponse

hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as follows:

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

rSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as follows:

- A post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8
- A post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8

4.4.2 Safety

4.4.2.1 Solicited Reactions

4.4.2.1.1 Daily Intensity

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

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

1) Solicited reactions (except Fever/Pyrexia) with an Investigator presence recorded as “No” and with all daily records missing, then all daily intensities will be derived as None
2) For a temperature partially missing after decimal point, the data will be analyzed replacing “MD” (missing data) by zero. For example, a “39.MD” daily temperature will be considered as "39.0°C" at the time of analysis.
3) For non-measurable (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 maximum intensity on the ongoing period is derived from the record of the maximum intensity / measurement after the end of the solicited period following the rule described above.

4.4.2.1.2 Maximum Overall Intensity

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

4.4.2.1.3 Presence

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

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

- Missing: Missing presence

Subjects with at least 1 non-missing presence (maximum overall intensity ≥ 0) for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

4.4.2.1.4 Time of Onset

Time of onset is derived from the daily intensities as described in Section 4.4.2.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3 during the solicited period (D0 to D07) after vaccination(s).

Note: If a reaction is not continuous (ie, reaction occurs over 2 separate periods of time intervened by at least 1 daily intensity Missing or None) then the time of onset is the first day of the first occurrence during the solicited period (D0 to D07) after vaccination(s).

4.4.2.1.5 Number of Days of Occurrence

Number of days of occurrence over the solicited period (D0 to D07) considered is derived from the daily intensities as described in Section 4.4.2.1.1. It corresponds to the number of days with 1 of daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity (eg, Grade 3) may also be derived.

4.4.2.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence after vaccination(s) is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

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

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

4.4.2.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period as described in Section 4.4.2.1.1 and the maximum intensity on the ongoing period. The Investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

If the last daily intensity at D07 of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

4.4.2.2 Unsolicited Non-serious Adverse Events

4.4.2.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not Grade 0 (None) intensity event.

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

4.4.2.2.2 Intensity

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

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

If the unsolicited non-serious AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule as the intensity scales defined in the Section 4.4.2.1.1 for that measurable injection site or systemic reaction.

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

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

4.4.2.2.3 Last Vaccination

Last vaccination before any unsolicited non-serious AE is the study vaccination at Visit 1 (D0).

4.4.2.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

Start date of the unsolicited non-serious AEs – date of last vaccination

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

The unsolicited non-serious AEs will be analyzed "Within 30 days", which corresponds to AEs with a time of onset between D0 and D30 after vaccination(s) or missing. An AE with missing time of onset will be considered to have occurred just within 30 days after the vaccination indicated by the visit number, so will be included in the safety analysis.

Note: Unsolicited non-serious AEs that occurred before vaccination (negative time of onset) or with onset higher than defined above (eg, > 30 days after vaccination[s]) will not be included in the safety analysis, but will be listed separately.

4.4.2.2.5 Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

Stop date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if 1 or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

4.4.2.3 Serious Adverse Events (including Adverse Events of Special Interest)

4.4.2.3.1 Last Vaccination

Last vaccination before an SAE (including AESIs) is the study vaccination at Visit 1 (D0).

4.4.2.3.2 Time of Onset

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

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

- Within 7 days after vaccination(s)
- Within 30 days after vaccination(s)
- During 6-month follow-up period: from D31 to the last telephone call on D180 (+ 14 days)
- During the entire study period: from D0 to the last telephone call on D180 (+ 14 days) (ie, all SAEs [including AESIs] occurred during the study)

An SAE (including AESI) with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

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

4.4.2.3.3 Duration

Duration will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.2.2.5.

4.4.2.4 Medically-Attended Adverse Events

MAAEs that occur within 30 days after vaccination(s) will be collected as unsolicited AEs. Unsolicited AEs that occur within the unsolicited period (within 30 days after vaccination[s]) or outside of the unsolicited period (from D31 to the 6-month follow-up telephone call on D180 [+ 14 days]) and have action taken of "Health care provider contact" will be summarized and presented as MAAEs. MAAEs will also be recorded in a MA from D30 after vaccination(s), until the 6-month follow-up telephone call on D180 (+ 14 days).

4.4.2.4.1 Last Vaccination

Last vaccination will be derived using the same methodology as used for unsolicited non-serious AEs described in Section 4.4.2.2.3.

4.4.2.4.2 Time of Onset

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

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

- Within 30 days after vaccination(s)
- During 6-month follow-up period: from D31 to the last telephone call on D180 (+ 14 days)

An MAAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in the safety analysis tables mentioned above.

4.4.2.4.3 Duration

Duration will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.2.2.5.

4.4.2.5 Other Safety Endpoints

4.4.2.5.1 Pregnancy

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

4.4.2.5.2 Action Taken

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

4.4.2.5.3 Seriousness

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

4.4.2.5.4 Outcome

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

4.4.2.5.5 Causality

There are 3 terms in our study indicating if there is a causal relationship between an AE and study vaccine (MenACYW conjugate vaccine, Trumenba vaccine, and Bexsero vaccine). It includes

"Relationship to Investigational Medicinal Product (IMP)" which refers to the relationship with MenACYW conjugate vaccine, "Relationship to Non-Investigational Medicinal Product (non-IMP)" which refers to the relationship with Trumenba vaccine or Bexsero vaccine, and "Relationship to Study Procedures" which is applicable for SAEs only. This information will be summarized as collected.

Variable "Relationship" which stands for the overall relationship and encompasses the "Relationship to IMP" and "Relationship to Study Procedures" will be derived in the tables and listings according to the following rules in this study:

- For all solicited reactions, the overall relationship will be derived as "Related"
- For all unsolicited injection site reactions, the overall relationship will be derived as "Related"
- For unsolicited non-serious systemic AEs,

  If "Relationship to IMP" is ticked as "Related" or missing, the overall relationship should be derived as "Related"; otherwise the overall relationship should be derived as "Not Related".

- For unsolicited serious systemic AEs,

  If any of "Relationship to IMP" and "Relationship to Study Procedures" is ticked as "Related" or missing, the overall relationship should be derived as "Related"; otherwise the overall relationship should be derived as "Not Related".

4.4.2.5.6 Adverse Events Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to study discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination "Serious Adverse Event" or "Other Adverse Event" is checked
- Safety overview table: A subject who has either the reason for early termination "Serious Adverse Event" or "Other Adverse Event" checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked on the termination form, that is at least Grade 1 and is within the time period indicated
- System Organ Class/Preferred Term (SOC/PT) table: An event (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked that is at least Grade 1 and is within the time period indicated

4.4.3 Derived Other Variables

4.4.3.1 Years Elapsed since Priming Vaccination Received in Either MET50, MET43, or Outside of Sanofi Pasteur Trials

Years ($3 \leqslant$ years < 4, $4 \leqslant$ years < 5, or $5 \leqslant$ years $\leqslant 6$) elapsed since priming vaccination is computed as follows: (Date of Vaccination in MET59 – Date of Vaccination in MET50, MET43, or outside of Sanofi Pasteur trials + 1) / 365.25

4.4.3.2 Race for Subgroup Analyses

Race for subgroup analyses will be categorized as:

- White
- Asian
- Black or African American
- Other

Note: The original race categories collected in CRF will still be used for demographics analyses. The American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Mixed origin, Not Reported and Unknown will be classified to "Other" stratum for subgroup analysis purpose only.

4.4.3.3 Subject Duration

The duration of a subject in the study is computed as follows: Maximum (Date of last visit, Date of term form) – (Date of D0 Visit) + 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 date of follow-up contact) – (Date of D0 Visit) +1.

4.4.3.4 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 D0 Visit) + 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 D0 Visit) + 1.

4.4.3.5 Protocol-prohibited Therapy, Medication or Vaccines

In general, the "prohibited" variable is not derived. All concomitant medications are reviewed by the clinical team and the value of "prohibited" variable is determined before database lock by the clinical team according to the following rules:

Only two categories of reportable medications will be considered as prohibited/restricted therapy, medication or vaccine:

Category 2:

- Flu vaccines administered within 14 days pre or post each trial vaccination, including the day of the study visit vaccination
- Other vaccines not included as study vaccines, it means non-study vaccines (e.g. Oral poliovirus, Yellow fever, Japanese encephalitis, or other routine/not-routine vaccine not described in the protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study visit vaccination
- Immune globulins, blood or blood-derived products and Immunosuppressive therapy, as described in the protocol

Category 3:

- Antibiotics that the subject received within the 72 hours preceding each Visit for blood draw related to IMP assessment (meningococcal vaccines)

If the above protocol-prohibited therapy, medication or vaccines are received at specific visits, it will impact the corresponding immunogenicity analyses.

The impact on each Per-Protocol Analysis Set (PPAS) is determined as the following:

- If the above protocol-prohibited therapy, medication or vaccines are received at D0 or D06, it will impact PPAS1.
- If the above protocol-prohibited therapy, medication or vaccines are received at D0 or D30, it will impact PPAS2.

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 (14), ie, using the inverse of the beta integral with SAS®). The CI of the difference in percentages will be computed using the Wilson Score method without continuity correction (15).

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (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 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, seroprotection, 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, and 95% CI of the geometric mean Graphical representation by Reverse Cumulative Distribution Curve (RCDC)

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective

5.1.1.1 Hypotheses

Thirty days after the administration of MenACYW conjugate vaccine, the sufficiency of the percentages of subjects who achieve an hSBA seroresponse* for meningococcal serogroups A, C, Y, and W in Group 1 and Group 2 will be tested.

Seroresponse will be considered sufficient if lower limit of the 1-sided 97.5% CI calculated using the exact method (Clopper-Pearson method) for percentage of subjects with hSBA seroresponse against serogroups A, C, Y, and W is greater than 75%. The study will be considered successful if the seroresponse sufficiency is demonstrated both in Group 1 and Group 2 separately.

This is equivalent to testing H0: $p \leq 0.75$ against H1: $p > 0.75$, where p is the observed proportion of subjects with hSBA seroresponse against serogroups A, C, Y, and W.

*hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as follows:

- 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

5.1.1.2 Statistical Methods

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (14), ie, using the inverse of the beta integral with SAS®).

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Hypotheses

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

5.1.2.2 Statistical Methods

5.1.2.2.1 For Secondary Objective 1

Six days after the administration of MenACYW conjugate vaccine, the hSBA vaccine seroresponse rates, seroprotection rates (hSBA titer ≥ 1:8), and hSBA GMTs between a subset of 50 subjects per Group 1 and Group 2 will be summarized and geometric mean titer ratio (GMTR) between the subset of 50 subjects per Group 1 and Group 2 will be calculated, and 95% CI will be provided.

5.1.2.2.2 For Secondary Objective 2

Thirty days after the administration of MenACYW conjugate vaccine alone, the hSBA vaccine seroresponse rates, seroprotection rates (hSBA titer ≥ 1:8), and the hSBA GMTs will be summarized and GMTR between Group 1 and Group 2 will be calculated, and 95% CI will be provided.

5.1.2.2.3 For Secondary Objective 3

Before the administration of MenACYW conjugate vaccine alone, 3-6 years after receiving the primary MCV4 vaccination, the hSBA GMTs will be summarized as well as seroprotection rates (hSBA titer ≥ 1:8) and GMTR between Groups 1, 3, and 4 and Group 2 will be calculated, and 95% CI will be provided.

5.1.2.2.4 For Secondary Objective 4

At baseline and D30, in subjects after having received a single dose of either MenACYW conjugate vaccine or Menveo vaccine, as part of study MET50 or MET43, the hSBA GMTs will be summarized as well as seroprotection rates (hSBA titer ≥ 1:8) and GMTR between MenACYW conjugate vaccine and Menveo vaccine groups will be calculated, and 95% CI will be provided. The GMTR between D0 of MET59 and D30 of MET50 (or MET43, if applicable) within MenACYW conjugate vaccine and Menveo vaccine groups will also be calculated, and 95% CI will be provided.

5.1.2.2.5 For Secondary Objective 5

Thirty days after the administration of MenACYW conjugate vaccine when administered alone or concomitantly with Trumenba vaccine or Bexsero vaccine, the vaccine seroresponse, seroprotection (hSBA titer ≥ 1:8), and hSBA GMTs will be summarized and GMTR between Group 1 and Group 3, between Group 1 and Group 4, and between Group 1 and pooled Groups 3 and 4 will be calculated, and 95% CI will be provided.

5.1.3 Statistical Methods for Observational Objectives

5.1.3.1 Hypotheses

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

5.1.3.2 Statistical Methods

Immunogenicity

Descriptive statistics will be provided for the hSBA antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine when it is administered alone or concomitantly with MenB vaccine for MenACYW conjugate vaccine-primed subjects and Menveo vaccine-primed subjects. Descriptive statistics will also be provided for the rSBA antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine when it is administered alone in a subset of 50 subjects per Group 1 and Group 2 (total of 100 subjects). In general, categorical variables 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) for percentages. For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

Reverse Cumulative Distribution Curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine treatment groups for MenACYW conjugate vaccine-primed subjects and Menveo vaccine-primed subjects.

In summary, descriptive analyses on A, C, Y, and W serogroups on D0, D06, and D30 after vaccination with MenACYW conjugate vaccine when it is administered alone or concomitantly with MenB vaccine using hSBA will include but not be limited to:

1) GMT and 95% CI
2) Titer distribution and RCDC
3) Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI
4) Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
5) Percentage of subjects with hSBA vaccine seroresponse*

*hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

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

Descriptive analyses on A, C, Y, and W serogroups on D0 and D30 after vaccination with MenACYW conjugate vaccine using rSBA will include but not be limited to:

1) GMT and 95% CI
2) Titer distribution and RCDC
3) Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
4) Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
5) Percentage of subjects with rSBA vaccine seroresponse*

*rSBA vaccine seroresponse is defined as a post-vaccination titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8.

Data of subjects from MET50 (or MET43, if applicable) and MET59 will be combined and paired to evaluate antibody persistence and overall trends over 3-6 years post-priming with an MCV4 (ie, MenACYW conjugate vaccine-primed subjects or Menveo vaccine-primed subjects). If Menveo vaccine-primed subjects that were not part of MET50 are recruited, those will not contribute to the assessment of antibody persistence.

Safety

Safety results in Section 4.3.2.2 will be described for subjects in all study groups. The main parameters for the safety endpoints will be described by 95% CIs (Clopper-Pearson method) (14). 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 vaccination(s) for all subjects in Groups 1 – 4	Percentage of subjects that have the event, MedDRA terms, intensity, relationship to vaccine, study discontinuation
Solicited injection site reactions	Within 7 days after vaccination(s) for all subjects in Groups 1 – 4	Percentage of subjects that have the event, onset, duration, intensity, action taken, study discontinuation, temperature collection routes
Solicited systemic reactions	Within 7 days after vaccination(s) for all subjects in Groups 1 – 4	
Unsolicited non-serious AE/AR	Within 30 days after vaccination(s) for all subjects in Groups 1 – 4	Percentage of subjects that have the event, MedDRA terms, onset, duration, intensity, relationship, action taken, study discontinuation

AEs leading to study discontinuation	Within 30 days after vaccination(s) for all subjects in Groups 1 – 4 During the entire study period (ie, D0 to the 6-month follow-up telephone call on D180 [+14 days]) for all subjects in Groups 1 – 4	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, study discontinuation
SAE (including AESI)	Within 7 days after vaccination(s) for all subjects in Groups 1 – 4 Within 30 days after vaccination(s) for all subjects in Groups 1 – 4 During 6-month follow-up after vaccine injection (ie, D31 to the 6-month follow-up telephone call on D180 [+14 days]) for all subjects in Groups 1 – 4 During the entire study period (ie, D0 to the 6-month follow-up telephone call on D180 [+14 days]) for all subjects in Groups 1 – 4	Percentage of subjects that have the event, MedDRA terms, onset, duration, relationship, seriousness criteria, outcome, study discontinuation
MAAE	Within 30 days after vaccination(s) for all subjects in Groups 1 – 4 (as unsolicited AE) D31 to 6-month follow-up telephone call, ie, D180 (+14 days) after vaccination(s) for all subjects in Groups 1 – 4	Percentage of subjects that have the event, MedDRA terms, onset, duration, relationship, seriousness criteria, outcome, study discontinuation

5.1.4 Complementary Output

Additional subgroup analyses by number of years ($3 \leqslant$ years < 4, $4 \leqslant$ years < 5, $5 \leqslant$ years $\leqslant 6$) elapsed since priming vaccination received in either clinical studies MET50, MET43, or outside of Sanofi Pasteur trials, age group (13 to 17 years and 18 to 26 years), gender (Female and Male), and race (White, Asian, Black or African American, and Other) will be provided in Appendix 15 of the CSR.

Demographics analyses by number of years since primed vaccines only:

- Baseline demographics – All Randomized or Assigned Subjects
- Baseline demographics – Per-Protocol Analysis Set 1
- Baseline demographics – Per-Protocol Analysis Set 2
- Baseline demographics – Safety Analysis Set

Immunogenicity analyses (tables and figures):

- hSBA GMTs and 95% CI at D0 and D30 for each group – Per-Protocol Analysis Set 2
- hSBA GMTs and 95% CI at D0 and D06 for Groups 1 and 2 – Per-Protocol Analysis Set 1
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA and 95% CI at D30 for each group – Per-Protocol Analysis Set 2
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA and 95% CI at D06 for Groups 1 and 2 – Per-Protocol Analysis Set 1
- hSBA titer ≥ 1:4 and ≥ 1:8 (vaccine seroprotection) against meningococcal serogroups A, C, Y, and W and 95% CI at D0 and D30 for each group – Per-Protocol Analysis Set 2
- hSBA titer ≥ 1:4 and ≥1:8 (vaccine seroprotection) against meningococcal serogroups A, C, Y, and W and 95% CI at D0 and D06 for Groups 1 and 2 – Per-Protocol Analysis Set 1
- rSBA GMTs and 95% CI at D0 and D30 for Groups 1 and 2 – Per-Protocol Analysis Set 2
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by rSBA and 95% CI at D30 for Groups 1 and 2 – Per-Protocol Analysis Set 2
- rSBA titer ≥ 1:8 and ≥ 1:128 against meningococcal serogroups A, C, Y, and W and 95% CI at D0 and D30 in Groups 1 and 2 – Per-Protocol Analysis Set 2

Safety analyses:

Safety overview after injection – Safety Analysis Set

Analysis to assess the impact of COVID-19:

- 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 identify and focus on the subset of subjects that were impacted by COVID-19
  - Defined as the subjects with at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19 or who reported "VISIT NOT DONE" for safety follow up in pandemic form: The intention is to consider only relevant impacts on subjects (minor protocol deviations are not taken into account)
  - To summarize disposition across study visits for these subjects

- To provide an individual listing of these subjects and how they were impacted
- To assess the potential impact of COVID on treatment effect by replicating the tables addressing the primary immunogenicity and main safety endpoints in the subsets of impacted / non-impacted subjects

5.2 Analysis Sets

Five analysis sets will be used: the Full Analysis Set (FAS1 for D06, FAS2 for D30, and FAS3 for antibody persistence analyses), the Per-Protocol Analysis Sets (PPAS1 for D06 and PPAS2 for D30), and the Safety Analysis Set (SafAS).

5.2.1 Full Analysis Set

5.2.1.1 Full Analysis Set 1 and Full Analysis Set 2

The FAS is defined as the subset of subjects who received at least 1 dose of the study vaccine and had a valid post-vaccination serology result. Two FASs will be defined (FAS1 for D06 and FAS2 for D30). All subjects will be analyzed according to the treatment group to which they were randomized or assigned.

5.2.1.2 Full Analysis Set 3

The FAS3 is defined as a subset of subjects who had a valid pre-vaccination serology result for antibody persistence analyses.

5.2.2 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. Two PPASs will be defined (PPAS1 for D06 and PPAS2 for D30). The subjects presenting with at least 1 of the following relevant protocol deviations will be excluded from the PPAS1 or PPAS2 as applicable:

- Subject did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria
- Subject did not receive vaccine(s)
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited Category 2 or Category 3 therapy / medication / vaccine
- Subject had other protocol violation that affected the subject's immune response, as determined by the clinical team prior to locking the database.

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

5.2.3 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. All subjects will have their safety analyzed according to the vaccine(s) they actually received at D30; either MenACYW conjugate vaccine alone or concomitantly with the MenB vaccines.

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

5.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS1 or PPAS2. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS1 or FAS2, according to randomized or assigned group. Antibody persistence analyses will be performed on the FAS3.

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

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

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

5.3.1.1 Immediate

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

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

5.3.1.2 Causality

Missing causality (relationship) for AEs will be handled as described in Section 4.4.2.5.5.

[a] For which safety data are scheduled to be collected

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.2.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.2.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If 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 visit collected.

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

5.3.2 Immunogenicity

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

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

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

The derived endpoint of fold-rise is computed 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

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

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

A total of 600 subjects will be enrolled. An estimated 15% drop-out rate from enrollment will result in approximately 510 subjects in the PPAS2 available for immunogenicity analyses. The total number of subjects targeted for enrollment in Group 1 (N=200) and Group 2 (N=200) will contribute to the safety database of MenACYW conjugate vaccine given as a booster vaccine.

For the Primary Objectives:

With 89 evaluable subjects per group in Group 1 and Group 2, the trial will have around 96% power to achieve the primary hypothesis for each serogroup, assuming independent seroresponses to each serogroup and between and within subjects.

Table 5.3: Power of the study based on the primary objectives with 89 evaluable subjects per Group 1 and Group 2

Antigen	Endpoint	Estimates for Group 1*	Estimates for Group 2†	Power (%)
A	Seroresponse	0.922	0.896	96
C	Seroresponse	0.971	1	> 99
Y	Seroresponse	0.974	1	> 99
W	Seroresponse	0.982	0.979	> 99
Overall				**96**

*Estimated responses are based on the results of MET56 Group 1 that received 1 dose of MenACYW conjugate vaccine.

†Estimated responses are based on the results of MET56 Group 1 Menveo-primed subjects that received 1 dose of MenACYW conjugate vaccine.

This study will include 200 subjects in Group 1 and Group 2 to build the MenACYW conjugate vaccine safety of booster database.

5.6 Data Review for Statistical Purposes

Review of the data has been anticipated through the data review process led by data management before database lock. This review of the data will include a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

The analysis set FAS3 is added in the SAP. FAS3 will be used to evaluate the antibody persistence 3-6 years after the priming vaccination with either MenACYW conjugate vaccine or the licensed vaccine Menveo®.

No other significant change occurred during the conduct of the trial not documented in a protocol amendment.

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