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

Clinical Trial Protocol, Amendment 2

Health Authority File Number:	BB-IND #: 14171
WHO Universal Trial Number (UTN):	U1111-1217-2137
Trial Code:	MET59
Development Phase:	Phase IIIb
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form/Route:	Liquid Solution/Intramuscular (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
Manufacturer:	Same as Sponsor
Coordinating Investigator:	[redacted]
Sponsor's Responsible Medical Officer:	[redacted]

Global Safety Officer: [redacted]

Regional Trial Manager:

Version and Date of the Protocol: Amendment 2, Version 7.0 dated 10 April 2020

History of Protocol Versions

Version*	Date	Comments
1.0	24 March 2019	Internal version, was not submitted
2.0	24 March 2019	Internal version, was not submitted
3.0	01 May 2019	Internal version, was not submitted
4.0	**03 May 2019**	**First version used in the study**
5.0	**22 January 2020**	**Protocol Amendment 1**
6.0	06 April 2020	Was to be Protocol Amendment 2 – Not published. Approved protocol version 6.0 underwent a minor edit in Section 9.3.2.3.3 and was reapproved and published as version 7.0

* Versions in bold font have been approved by the Independent Ethics Committee(s) (IEC[s]) / Institutional Review Board(s) (IRB[s]) and used in the study.

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	MenACYW Conjugate Vaccine
Active Substances:	Capsular polysaccharide from meningococcal serogroups A, C, Y, and W conjugated to tetanus toxoid

Title of the Study:	Immunogenicity and Safety of a Booster Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults
Development Phase:	Phase IIIb
Coordinating Investigator:	[redacted]
Study Sites:	This will be a multi-center study conducted in up to 40 sites in the United States (US) and Puerto Rico. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Q3 2019 to Q1 2020
Study Design, Schedule of Study Procedures, and Methodology:	This will be 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 MenACYW conjugate vaccine or the licensed vaccine Menveo®, and to evaluate the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine when administered alone or concomitantly with licensed meningococcal serogroup B (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 the MET50 study 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®, N=100; and Group 4, MenACYW conjugate vaccine + Bexsero®, 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 Groups 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). 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 protocol.
	Blood sampling All subjects will provide a pre-vaccination (baseline) blood sample on D0 and a post-vaccination 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 sample on D06 (±1 day). This subset will have 3 visits in total. Collection of safety data Safety data will be collected as follows: Immediate unsolicited systemic adverse events (AEs) will be collected within 30 minutes after vaccination. Solicited AEs will be collected from D0 to D07 after vaccination; unsolicited AEs will be collected from D0 to D30 after vaccination; serious adverse events (SAEs) (including adverse events of special interest [AESIs]) will be collected throughout the study from D0 through D180 after vaccination. Medically-attended adverse evets (MAAEs) will be collected from D30 until the end of the 6-month follow-up period, ie, D180 (+14 days) after vaccination(s).
Interruption of the Study:	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the (IECs) / (IRBs), or the governing regulatory authorities in the US where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory

	requirements. The Investigators shall promptly inform the study subjects/subject's parents/guardians and should assure appropriate subject therapy and/or follow-up. There will be an internal team at the level of the Sponsor (Safety Management Team, [SMT]), which will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in both recruitment and / or further vaccination while it investigates any potential signs or concerns.
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
Primary Endpoints:	1. Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at baseline (D0, pre-vaccination) and 30 days (+14 days) after vaccination in Group 1 2. Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at baseline (D0, pre-vaccination) and 30 days (+14 days) after vaccination in Group 2
Secondary Objectives:	1. To describe the vaccine seroresponse, seroprotection (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 D0 (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 of 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)
Secondary Endpoints:	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)

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
Observational Endpoints:	**Immunogenicity** 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) **Safety** 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 case report book [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
Planned Sample Size:	A total of approximately 600 subjects are planned to be enrolled as follows: Group 1 (MenACYW conjugate vaccine-primed): n = 200 Group 2 (Menveo vaccine-primed): n = 200 Group 3 (MenACYW conjugate vaccine-primed): n = 100 Group 4 (MenACYW conjugate vaccine-primed): n = 100
Duration of Participation in the Study:	The duration of each subject's participation in the study will be approximately 180 days (+14 days). There will be a safety follow-up telephone call at 6 months (+14 days) after vaccination(s) at D0.
Investigational Product:	**MenACYW conjugate vaccine:** Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Form:	Liquid solution
Composition:	Each 0.5 milliliter (mL) dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients: Meningococcal capsular polysaccharides: Serogroup A.....10 micrograms (µg) Serogroup C..... 10 µg Serogroup Y..... 10 µg Serogroup W..... 10 µg Tetanus toxoid protein carrier.....approximately 55 µg* *Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation
Route:	Intramuscular (IM)
Batch Number:	To be determined
Other Product 1:	**Trumenba vaccine**: Meningococcal Group B Vaccine (Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc., Philadelphia, PA, USA)
Form:	Liquid suspension
Composition:	Each 0.5 mL dose of vaccine contains recombinant lipidated factor H binding protein (fHBP) variants from *Neisseria meningitidis* (*N meningitidis*) group B: • fHBP subfamily A: 60µg • fHBP subfamily B: 60µg • PS80: 0.018 mg • Al^{3+} as AlPO4 in histidine buffered saline: 0.25 mg
Route:	IM

Batch Number:	To be determined
Other Product 2:	**Bexsero vaccine**: Meningococcal group B Vaccine (recombinant deoxyribonucleic acid [rDNA], component, adsorbed) (GSK Vaccines, Srl, Sovicille (SI), Italy)
Form:	Suspension for injection in pre-filled syringe
Composition	Each 0.5 mL dose contains: Recombinant *N meningitidis* group B NHBA fusion protein*†‡ 50 µg Recombinant *N meningitidis* group B NadA protein*†‡ 50 µg Recombinant *N meningitidis* group B fHbp fusion protein*†‡ 50 µg Outer membrane vesicles from *N meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA Pl.4† 25 µg *Produced in E. coli cells by recombinant DNA technology †Adsorbed on aluminum hydroxide (0.5 mg Al3+) ‡ NHBA (Neisseria Heparin Binding Antigen), NadA (Neisseria adhesin A), fHbp (factor H binding protein). The vaccine contains the following excipients: sodium chloride, histidine, sucrose, water for injections.
Route	IM
Batch	To be determined
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1. Aged ≥ 13 to < 26 years on the day of inclusion 2. Subject participated in and completed study MET50 (MET50 Groups 1, 2, or 3 only) or study MET43 (MET43 Groups 1, 2, or 3 only) 3. For MET59 Group 2 only (Menveo vaccine-primed subjects only; enrichment population): Subjects have a documented record of having received 1 dose of Menveo vaccine 3-6 years earlier either as a part of a clinical trial or as routine vaccination. Subjects who participated in MET50 Group 4 can be enrolled if they fulfill this criterion 4. Subject aged 13 to < 18 years: assent form has been signed and dated by the subject and informed consent form (ICF) has been signed and dated by the parent or guardian 5. Subjects aged ≥ 18 (or legal age of majority, if different from 18 years of age) to < 26 years: ICF has been signed and dated by the subject 6. Subject aged 13 to < 18 years: both the subject and parent or guardian are able to attend all scheduled visits and to comply with all trial procedures 7. Subjects aged ≥ 18 (or legal age of majority, if different from 18 years of age) to < 26 years: able to attend all scheduled visits and to comply with all trial procedures

Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1. Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 4 weeks after the last vaccination. To be considered of non-childbearing potential, a female must be pre-menarche, or post-menopausal for at least 1 year, or surgically sterile 2. Participation in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure 3. Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine before D30 except for influenza vaccination, which may be received at least 2 weeks before study investigational vaccine 4. Receipt of immune globulins, blood or blood-derived products in the past 3 months 5. Receipt of any meningococcal vaccine including a licensed or investigational MenACWY vaccine or MenB vaccine since participation in study MET50 or MET43 6. Menveo vaccine-primed subjects only (enrichment group for Group 2): receipt of more than 1 dose of Menveo vaccine or vaccination with another licensed or investigational MenACWY vaccine or with a licensed or investigational MenB vaccine 7. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months) 8. History of meningococcal infection, confirmed either clinically, serologically, or microbiologically 9. At high risk for meningococcal infection during the trial (specifically but not limited to subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease). 10. Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances 11. Personal history of Guillain-Barré syndrome (GBS) 12. Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within at least 10 years of the proposed study vaccination 13. Verbal report of thrombocytopenia, contraindicating intramuscular vaccination 14. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination 15. Deprived of freedom by an administrative or court order, or in an

	emergency setting, or hospitalized involuntarily 16. Current alcohol abuse or drug addiction 17. Chronic illness (eg, HIV, hepatitis B, hepatitis C) that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion 18. Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided 19. Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 20. Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
Statistical Methods:	All immunogenicity analyses will be performed on the Per-Protocol Analysis Sets (PPAS1 for D06 and PPAS2 for D30). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set. All safety analyses will be performed on the Safety Analysis Set. **Primary Objectives** 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% confidence interval (CI) calculated using the Exact method (Clopper-Pearson method) for percentage of subjects with hSBA seroresponse against serogroups A, C, W and Y is greater than 75%. The study will be considered successful if the seroresponse sufficiency is demonstrated both in Group 1 and Group 2 separately. *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.
	Secondary Objectives • 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. • 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.

	• 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. • 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. • 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.
	Observational Objectives ***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 when it is administered alone for 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 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 (for Groups 1 and 2 only), 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: • GMT and 95% CI • Titer distribution and RCDC • Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with hSBA vaccine seroresponse*

*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 is not be limited to:

- GMT and 95% CI
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with rSBA vaccine seroresponse†

† 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 from 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.

Additional subgroup analyses of the hSBA vaccine seroresponse rates, hSBA titer ≥ 1:4 and ≥ 1:8, hSBA GMTs, rSBA vaccine seroresponse rates, rSBA titer ≥ 1:8 and ≥ 1:128, and rSBA GMTs will also be provided by number of years (3 years, 4 years, 5 years, and 6 years) 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).

Safety

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

The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions occurring from D0 to D07 after each vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken. Since MenACYW conjugate vaccine and the concomitant MenB vaccines will be administered in different limbs, solicited injection site reactions can be distinguished between the two products, and will be analyzed and presented separately.

Immediate unsolicited systemic AEs and unsolicited AEs occurring up to D30 after each vaccination will be summarized.

The number and percentage of subjects reporting any unsolicited non-serious AEs will be summarized by study group, intensity, time of onset period, duration, and by MedDRA preferred term and system organ class (SOC), as well as by relationship to the study vaccine.

The number and percentage of subjects reporting at least one of any MAAEs

will be summarized throughout the trial.

The number and percentage of subjects reporting at least one of any SAEs will be summarized by study group, seriousness criterion, outcome, and by MedDRA preferred term and SOC, as well as by relationship to the study vaccine.

The number and percentage of subjects reporting at least one of any AESIs will be summarized throughout the trial.

Exact (Clopper-Pearson) 2-sided 95% CIs will be calculated for the percentages.

Additional subgroup safety analyses will also be provided by number of years (3 years, 4 years, 5 years, and 6 years) 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).

Calculation of Sample Size

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

Table S1: Power of the study based on the primary objectives with 89 evaluable subjects per group in 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 booster 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.

Table of 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		BL0003	
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	

Visit/Contact	Visit 1	Telephone Call 1	Visit 2†	Telephone Call 2†
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 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)

Table of 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				
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	

Visit/Contact	Visit 1	Visit 2	Telephone Call 1	Visit 3	Telephone Call 2†
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).

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ACIP	Advisory Committee on Immunization Practices
AR	adverse reaction
CDM	Clinical Data Management
CI	confidence interval
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CTA	clinical trial agreement
CTL	Clinical Team Leader
EDC	electronic data capture
FAS	full analysis set
FDA	US Food and Drug Administration
fHBP	factor H binding protein
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global Pharmacovigilance
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMD	Invasive meningococcal disease
IME	important medical event
IND	investigational new drug (application)
IRB	Institutional Review Board
IRT	interactive response technology
LCLS	last contact, last subject
LLOQ	lower limit of quantification

LLT	lowest level term
MAAE	medically-attended adverse event
MCV4	quadrivalent meningococcal conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
RCDC	Reverse cumulative distribution curve
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SAP	statistical analysis plan
SafAS	safety analysis set
SBA	serum bactericidal assay
SMT	Safety management team
TMF	trial master file
ULOQ	upper limit of quantification
WHO	World Health Organization

1 Introduction

1.1 Background

This trial will evaluate the antibody persistence 3-6 years after the priming vaccination with the 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 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). Serogroup B is responsible for endemic disease and some outbreaks, while serogroup C is responsible for large outbreaks (5). Serogroup A is the main cause of epidemics in the world and is especially dominant in Africa and Asia. Serogroup W has been observed in Africa, as well as the United Kingdom, in residents who participated in the Hajj pilgrimage to the Kingdom of Saudi Arabia (4) (6) (7) and more recently in Chile (8), Turkey (9) (10), China (11) (12), Argentina (13), and Brazil (14) (15), and in other parts of the world. Serogroup X causes substantial meningococcal disease in parts of Africa, but rarely causes disease in other parts of the world (2) (16). Serogroup Y has not been associated with outbreaks, but its frequency as a cause of sporadic cases has gradually increased in the US and more recently in Canada and Europe (17) (18) (19). This serogroup is commonly associated with meningococcal pneumonia, particularly in older adults ≥ 65 years of age (20). Outbreaks of serogroup B meningococcal disease have also been reported on college campuses in the US during the last six-year period: a prolonged outbreak of serogroup B on a university campus in Ohio from 2008-2010 and 2 universities in New Jersey and California in 2013 (21) (22).

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 year old group. The highest incidence rate in Europe is caused by serogroup B, followed by C (23). The highest proportion of meningococcal cases was due to serogroup B in the population under 5 years of age. The highest proportion of serogroup C cases was observed in the population 25 to 44 years of age while the proportion of serogroup Y cases was highest in the population aged 65 years and above.

Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in 2013-2014 compared with an average of 1% to 2% of all IMD cases in earlier years (24). A gradual increase in serogroup Y IMD has also been recently reported in Sweden during 2005-2012 (25) (26). Nearly 50% of all IMD was caused by serogroup Y in 2012 (25). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Nordic countries, accounting for 31% in Norway in 2009-2010 and 38% in Finland in 2010 (27).

In the US, the incidence rate of IMD was 0.14 per 100,000 in all ages, 0.83 per 100,000 in infants less than 1 year, 0.62 per 100,000 in 1 year of age, 0.27 per 100,000 in 2 to 4 years of age, and 0.02 per 100,000 in children aged 5 to 17 years in 2013. The age specific incidence rate per 100,000 was 0.08 in 50 to 64 years, 0.03 in 65 to 74 years, 0.14 in 75 to 84 years, and 0.43 in 85 years and older in 2013 (28).

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

1.2 Background of the Investigational Product

1.2.1 Clinical Studies

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 that 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 EU region (Spain, Germany, Hungary and Finland), and MET57 was conducted in Thailand, South Korea, Russia, and Mexico.

The following are summaries of the completed studies conducted in the adolescent and adult population (10 to 55 years old) using the current vaccine formulation:

1.2.1.1 Study MET50 (Phase II)

Study MET50 was a Phase II, open-label (the laboratory technicians were blinded to group assignment), randomized, parallel-group, controlled, multi-center study to evaluate the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine compared to that of the licensed vaccine, Menveo vaccine and when MenACYW conjugate vaccine was given with Tdap (tetanus, diphtheria, and acellular pertussis) and HPV (human papilloma virus) vaccines, in healthy adolescents 10 through 17 years of age in the US.

Subjects received vaccine(s) according to the following schedule in Table 1.1. Subjects in all groups provided a pre-vaccination blood sample at Visit 1 (D0) and a post-vaccination sample at

Visit 2 (23 to 37 days after the vaccination at Visit 1). Subjects in Group 3 and Group 4 provided an additional blood sample at D210 (Visit 5, 23 to 37 days after HPV vaccination at Visit 4).

Table 1.1 MET50 study groups and vaccination schedule

Group	D0, Visit 1	D60, Visit 3	D180, Visit 4
1	MenACYW conjugate vaccine	NA	NA
2	Menveo vaccine	NA	NA
3	MenACYW conjugate vaccine Tdap, HPV	HPV	HPV
4	Tdap, HPV	HPV	HPV

Abbreviation: NA, not applicable

A total of 503 subjects in Group 1 received MenACYW conjugate vaccine, 501 subjects in Group 2 received Menveo vaccine, 392 subjects in Group 3 received MenACYW conjugate vaccine along with Tdap + HPV vaccines, and 296 subjects in Group 4 received Tdap + HPV vaccines and were included in the Safety Analysis Set.

In this study, the following immunogenicity and safety conclusions were reached:

Immunogenicity Conclusions

MenACYW conjugate vaccine was non-inferior to Menveo vaccine as measured by the hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was more than -10%.

MenACYW conjugate vaccine and Menveo vaccine induced comparable immune responses as measured by the rSBA vaccine seroresponse

MenACYW conjugate vaccine administered concomitantly with Tdap and HPV vaccines was non-inferior when compared to MenACYW conjugate vaccine administered alone as measured by hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was more than -10%.

The anti-pertussis responses of the Tdap vaccine administered concomitantly with MenACYW conjugate vaccine and HPV vaccine versus Tdap vaccine administered concomitantly with HPV vaccine only was non-inferior for the PT antigen but did not meet non-inferiority for the FHA, PRN, and FIM antigens

The anti-tetanus and anti-diphtheria responses of the Tdap vaccine administered concomitantly with MenACYW conjugate vaccine and HPV vaccine versus Tdap vaccine administered concomitantly with HPV vaccine alone were non-inferior as measured by the percentages of subjects who achieved ≥ 1.0 IU/mL anti-tetanus or anti-diphtheria antibody concentrations

The non-inferiority of HPV vaccine after the 3-dose series when the first dose was administered concomitantly with MenACYW conjugate vaccine and Tdap vaccine compared to when the first dose of HPV vaccine was administered with Tdap vaccine alone as measured by the GMTs and by the percentages of subjects achieving seroconversion for anti-HPV6, HPV11, HPV16, and HPV18 antibody titers was demonstrated.

Safety Conclusions

Overall, vaccination with MenACYW conjugate vaccine among adolescents was found to be safe with no safety concerns identified when given alone or concomitantly with Tdap and HPV vaccines. The MenACYW conjugate vaccine was well tolerated with no immediate hypersensitivity reactions and no related SAEs.

The safety profile of MenACYW conjugate vaccine was comparable to that of the licensed Menveo vaccine when given alone, while the systemic reactogenicity was found to be higher when MenACYW conjugate vaccine was given with Tdap and HPV vaccines. However, reactogenicity remained comparable to that observed with the control Group 4, when the licensed concomitant vaccines were given without MenACYW conjugate vaccine.

The safety profiles of the concomitant licensed vaccines were comparable when administered with or without MenACYW conjugate vaccine.

No new clinically important findings were identified with administration of the MenACYW conjugate vaccine.

1.2.1.2 Study MET43 (Phase III)

MET43 was a Phase III study in 3344 adolescents and adults aged 10 through 55 years in the US to evaluate the immune lot consistency of MenACYW conjugate vaccine, evaluate the immune non-inferiority versus Menactra®, and describe the safety and additional immunogenicity of study vaccines.

Immune lot consistency was demonstrated between 3 lots of MenACYW conjugate vaccine.

Non-inferiority of immune response for all serogroups was also demonstrated after administration of 1 dose of MenACYW conjugate vaccine to subjects 10 through 55 years, subjects 10 through 17 years and subjects 18 through 55 years of age as compared to Menactra vaccine, based on vaccine seroresponse as evaluated by hSBA.

Vaccination with MenACYW conjugate vaccine among adolescents and adults aged 10 through 55 years was found to be well tolerated with no safety concerns identified. The safety profile of MenACYW conjugate vaccine was comparable to that of Menactra vaccine.

1.2.1.3 Study MET56 (Phase III)

MET56 was a Phase III study in 810 adolescents and adults aged at least 15 years in the US and Puerto Rico to describe the safety and antibody response to revaccination with MenACYW conjugate vaccine in persons who received their first MCV4 dose at ≥ 10 years of age. As Menactra vaccine is already licensed in the US for booster vaccination of individuals 15 through 55 years of age at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose, the study compared a single booster dose of MenACYW conjugate vaccine to a single booster dose of Menactra vaccine when given to adolescents and adults 4 to 10 years after being primed with 1 dose of MCV4. This time interval post-vaccination was selected to evaluate the booster responses in individuals that received MCV4 recently after its licensure in the US (Menactra vaccine was the first MCV4 licensed in the US in 2005); thus, the subjects would have

been up to 10 years post-priming, and completed the minimum time interval of 4 years for booster vaccination in adolescents and adults as per the prescribing information for Menactra vaccine.

Overall, the MenACYW conjugate vaccine demonstrated immune non-inferiority for all 4 serogroups based on seroresponse as measured by hSBA vs Menactra vaccine when given as a booster dose to adolescents and adults who had previously received an MCV4. This study provides critical data in the MCV4-primed population and provides evidence that a booster dose of MenACYW conjugate vaccine administered at least 4 years after an initial dose can elicit a strong immune response in adolescents and adults. These data also provide evidence that MenACYW conjugate vaccine is an effective booster vaccination, regardless of age or the MCV4 administered initially.

1.2.1.4 Persistence of antibody responses and booster assessment following meningococcal quadrivalent conjugate vaccines (MCV4)

The persistence of antibodies against meningococcus has been studied in individuals that have received quadrivalent meningococcal conjugated vaccines, and the results have revealed that immunity wanes over time. Vaccine effectiveness for Menactra vaccine was 82% (CI = 54% to 93%) for adolescents vaccinated < 1 year earlier, 80% (CI = 52% to 92%) for adolescents vaccinated 1 to < 2 years earlier, 71% (CI = 34% to 87%) for adolescents vaccinated 2 to < 3 years earlier, and 59% (CI = 5% to 83%) for adolescents vaccinated 3 to < 6 years earlier (29). In October 2010, the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) approved updated recommendations to include a booster dose of MCV4 at age 16 years for adolescents previously vaccinated at 11 to 12 years of age. For adolescents vaccinated at age 13 through 15 years, administration of a one-time booster dose is recommended, preferably at age 16 through 18 years. For those who are vaccinated with a primary dose of MCV4 at or after age 16 years, a booster dose is not recommended. The minimum interval between the first and booster dose recommended is 8 weeks (30).

At the time this recommendation was made, neither of the 2 licensed quadrivalent meningococcal conjugate vaccines available in the US (ie, Menactra vaccine and Menveo vaccine), were approved for use as a booster according to their respective Prescribing Information, although the safety and immunogenicity of booster doses of Menactra vaccine had been evaluated in the context of follow-up studies conducted at least 3 years after the first dose of the vaccine in a number of studies. To date, similar data have been generated for Menveo vaccine, but on a smaller scale. In 2014, on the basis of a US study involving more than 800 participants who received Menactra vaccine 4 to 6 years after a prior dose, Menactra vaccine was approved for use as a booster in the US. Currently, Menveo vaccine has not yet been approved for use as a booster in the US. In Europe, the summary of product characteristics for Menveo vaccine states that long-term antibody persistence data are available up to 5 years after vaccination and that the product may be given as a booster dose in subjects who have previously received primary vaccination with Menveo vaccine, other conjugated meningococcal vaccine or meningococcal unconjugated polysaccharide vaccine, and that the need for and timing of a booster dose in subjects previously vaccinated with Menveo vaccine is to be defined on the basis of national recommendations.

It is expected that after its licensure, MenACYW conjugate vaccine will replace Menactra vaccine over a period of time in many/all markets. As adolescents primed with Menactra vaccine or Menveo vaccine reach the recommended age for a booster quadrivalent meningococcal vaccine

(MCV4) vaccine, it is important that the US Prescribing Information (with the US being the country of origin for MenACYW conjugate vaccine) contains an indication aligned with the booster recommendations for use of MCV4 vaccines.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. There might be no direct benefit from receiving it. However, on the basis of the data from previous studies, evaluation of the immunogenicity profile of MenACYW conjugate vaccine in different age groups shows that the majority of subjects develop seroprotective levels of antibodies after vaccination. The safety evaluation indicates that the vaccine is well tolerated, and no safety issues have been detected to date. In all, the data support the further evaluation of MenACYW conjugate vaccine in humans.

The 2 MenB vaccines; Trumenba® (Pfizer) and Bexsero® (GlaxoSmithKline) (32) (33) are licensed for the protection of adolescents and adults between 10-25 years of age against invasive serogroup B meningococcal disease. In the European Union, Canada, and Australia, Bexsero vaccine is licensed for the protection of adults, adolescents, children, and infants as young as 2 months of age and Trumenba vaccine is licensed for use in individuals 10 years of age and older.

As with any vaccine, MenACYW conjugate vaccine, Trumenba vaccine or Bexsero vaccine may not protect 100% of individuals against the disease they are designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine, Trumenba vaccine or Bexsero vaccine may cause injection site reactions such as pain, swelling, and erythema, or certain systemic events such as fever, headache, malaise, or myalgia.

Other common reactions after Trumenba vaccine or Bexsero vaccine in the studied age group include injection site induration, fatigue, arthralgia, chills, and nausea.

There may be a rare possibility of an allergic reaction, which could be severe.

Guillain-Barré syndrome (GBS) has been reported mostly in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of a US licensed meningococcal conjugate vaccine (34). A retrospective cohort study carried out in the US using healthcare claims data found no evidence of increased GBS risk associated with the use of that vaccine. The study was able to exclude all but relatively small incremental risks (35).

A review by the Institute of Medicine (IOM) found inadequate evidence to accept or reject a causal relationship between tetanus toxoid-containing vaccines and GBS (36). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (37). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (38).

No occurrences of GBS, brachial neuritis or Arthus reaction have been reported with the use of MenACYW conjugate vaccine in the completed clinical trials.

In a previous study with MenACYW conjugate vaccine, 1 SAE of reactive arthritis reported in a toddler was considered by the Investigator to be related to the investigational vaccine. The subject developed right knee inflammation the day after receiving MenACYW conjugate vaccine, given by IM injection in the right deltoid. The subject recovered after treatment with ibuprofen and antibiotics. Results of the reactive arthritis investigations performed as part of the work up were not indicative of any specific diagnosis. A point of further consideration was the monoarticular nature of the inflammation in this subject; reactive arthritis would typically be present clinically in a polyarticular fashion. Importantly, no similar cases have been reported following the administration of MenACYW conjugate vaccine in any other trials.

The risk of vasovagal syncope exists after any vaccination, most commonly in the adolescent age group (39). A few cases of immediate vasovagal-like response or syncope have been observed in adolescent or young adult study participants who had received MenACYW conjugate vaccine. Procedures should be in place to prevent falling injury and manage syncopal reactions.

The potential risks associated with blood drawing include local pain, bruising and, rarely, fainting or infection.

There may be other risks for MenACYW conjugate vaccine that are not yet known. The potential risks listed here are not exhaustive. Refer to the package insert for Trumenba vaccine and Bexsero vaccine (32) (33), and the Investigator's Brochure for the investigational MenACYW conjugate vaccine for additional information regarding potential risks.

1.4 Rationale for the Study

Early Phase I/II trials including those with the final formulation (studies MET39, MET50, MET54, and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants, toddlers, adolescents, and older adults.

This study will be a follow-up study of MET50 mainly, but depending on enrollment rates of MenACYW conjugate vaccine-primed subjects (ie, if half of the planned sample size is not enrolled in the first 2 months), can include subjects from study MET43 who comply with the inclusion / exclusion criteria. Additionally, other individuals who were vaccinated with Menveo vaccine 3-6 years earlier outside of Sanofi Pasteur studies and who comply with the inclusion / exclusion criteria can be enrolled.

This study will measure the antibody persistence 3-6 years after priming with either MenACYW conjugate vaccine or Menveo vaccine, and describe the safety profile and immune response to revaccination (booster) with MenACYW conjugate vaccine in those individuals who as adolescents had received the primary dose of either MenACYW conjugate vaccine or Menveo® vaccine dose 3-6 years earlier. Subjects will therefore be within an age range of 13 to 25 years at the time of the booster vaccination (based on their age at enrollment in MET50 or MET43). The boostability of MenACYW conjugate vaccine in MenACYW conjugate vaccine-primed or Menveo vaccine-primed subjects will be determined by sufficiency of the seroresponse measured using hSBA 30 days post-booster. The sufficiency of the percentages of subjects who achieve an hSBA seroresponse for meningococcal serogroups A, C, Y, and W will be tested sequentially;

first in MenACYW conjugate vaccine-primed subjects, if met, also in Menveo vaccine-primed subjects. Seroresponse will be considered sufficient if the lower limit of the 1-sided 97.5% confidence interval (CI) for the percentage of subjects with hSBA seroresponse against serogroups A, C, W and Y is greater than 75%. The study will be considered successful if the seroresponse sufficiency is demonstrated at least in the group of subjects who received primary vaccination with MenACYW conjugate vaccine 3-6 years earlier.

Thus, 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 subjects who received the first vaccination with an MCV4 vaccine (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 Study 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 9.1.1.1.

2.2 Secondary Objectives

3. To describe the vaccine seroresponse, seroprotection (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)
4. 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 D0 (pre-vaccination) and D30 (+14 days) after vaccination with MenACYW conjugate vaccine alone (Groups 1 and 2)

5. 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
6. 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)
7. 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 9.2.1.1.

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 objectives are presented in Section 9.3.1.1.

3 Investigators and Trial Organization

This study will be conducted in up to 40 centers in the US and Puerto Rico. The Principal Investigators and any sub-Investigators at the individual sites will be coordinated by 1 Coordinating Investigator. Details of the trial centers, the Investigators at each center, and the Coordinating Investigator are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal safety management team (SMT) will perform a blinded safety analysis on safety data after vaccination.

The Sponsor's Responsible Medical Officer (RMO) (the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted].

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form (ICF) and the assent form, subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

The Investigator will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All serious adverse events (SAEs) occurring during the study that are related to the product administered will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study 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 meningococcal serogroup B (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).

5.1.2 Justification of the Study Design

This study is part of the ongoing development program that focuses on demonstrating that MenACYW conjugate vaccine can provide broad coverage against circulating meningococcal strains from serogroups A, C, Y, and W in infants through older adults. MET59 is a study that will be conducted as part of the Phase IIIb development of MenACYW conjugate vaccine in which the vaccine candidate will be evaluated as a booster dose in adolescents/young adults. This study will describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine given 3-6 years after a primary dose of MenACYW conjugate vaccine or Menveo vaccine was administered. This study will also describe the antibody persistence 3-6 years after primary vaccination prior to administration of the booster dose. Subjects who were included in study MET50 and MET43 are eligible to be enrolled in MET59.

5.1.3 Study 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 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 protocol.

Blood sampling

All subjects will provide a pre-vaccination (baseline) blood sample on D0 and a post-vaccination 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 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 AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB)
- The subject 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.
- SAEs (including AESIs) and MAAEs will be recorded throughout the study. The subject or subject's 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 from D30 until the 6-month (+14 days) follow-up phone call. The subjects or subject's 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 subject's 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 the subject's

participation in the study is discontinued, the information recorded on the diary card will be reviewed at this time and the diary card will be retrieved by the site.

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

5.1.4 Visit Procedures

Medical procedures (examinations, injections, etc.) must be conducted by appropriately licensed or credentialed study site staff working within the scope of their license / credentials.

D0 Visit: Inclusion, Randomization, Blood Sample, and Vaccination

1. **Subjects aged 13 to < 18 years[a]:** Give the subject and the subject's parent / guardian information about the trial, answer any questions, obtain signed assent from subjects and the written informed consent (signed as below) from the subject's parent / guardian, and give him / her a signed copy of each.

   Subjects aged 18 years[a] and older: Give the subject information about the trial, answer any questions, obtain signed informed consent form from subject, and give him / her a signed copy.
2. Check inclusion and exclusion criteria for eligibility
3. Collect demographic data
4. Urine pregnancy test (if applicable)
5. Obtain verbal medical history about the subject
6. Conduct a history-directed physical examination, including temperature (a physical examination conducted during the same day as part of routine clinical care may be used for this purpose)
7. Contact the interactive response technology (IRT) system for randomization (except for subjects primed with Menveo vaccine which are allocated automatically to Group 2), allocation of subject number, vaccine group assignment, and blood sample subset assignment
8. Obtain the blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (3 attempts), then Visit 1 can be rescheduled to a later date at which point informed consent and

[a] Or legal age of majority, if different from 18 years of age

inclusion/exclusion criteria must be re-validated. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.

9. Administer the MenACYW conjugate vaccine in the deltoid muscle. For subjects in Group 3 and Group 4, administer the concomitant vaccine in the opposite arm.
10. Keep the subject under observation for 30 minutes and record any AE in the source document.
11. Give the subject or subject's parent / guardian a diary card, a thermometer, and a ruler, and go over the instructions for their use.
12. Remind the subject or subject's parent / guardian to expect a telephone call 8 days after the D0 visit and to bring back the diary card when they return for the D30 (+14 days) visit at a specified date and time.
13. Remind the subject or subject's parent / guardian to notify the site in case of an SAE.
14. Complete the relevant (electronic) case report form CRF pages for this visit.

D06 Visit (D06 [+-1 day] after D0 visit (100-subject subset only): Blood sample

1. Review temporary contraindications for subsequent blood sampling.
2. Obtain the blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).

Telephone Call 1 (D08 [+2 days] after D0 visit)

Note: If D08 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1. Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2. Remind the subject or subject's parent / guardian to do the following:
   - Complete the D0 to D07 pages of the diary card.
   - Complete the remaining pages of the diary card and bring them to D30 (+14 days) visit.
   - Notify the site in case of an SAE.

D30 Visit (+14 days after D0): Collection of Safety Information and Blood Sample

1. If the diary card information from D0 to D07 has not yet been obtained, obtain it at this time. Review the pages of the diary card with the subject or the subject's parent / guardian, including any AEs, medications, or therapy that occurred since vaccination
2. Review temporary contraindications for subsequent blood sampling (see Section 5.2.7)
3. Obtain the blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples) before administration of a second MenB vaccination (applicable to Groups 3 and 4 only, and given outside of the objectives of the study)
4. Give the subject or the subject's parent / guardian an MA
5. Complete the relevant (electronic) case report form CRF pages for this visit (including the trial termination record).
6. If the subject or the subject's parent / guardian does not return for the D30 visit, and the diary card is not received at the site, site personnel will contact the subject or the subject's parent / guardian by telephone. During the telephone call, the subject or the subject's parent / guardian will be reminded to return the diary card to the study site. Telephone calls will be documented on the Telephone / Interview Record. If the study personnel are unable to contact the subject or the subject's parent / guardian with 3 attempts, the study personnel will follow instructions given in Section 5.2.9.

Safety Follow-up Telephone Call (D180 [+14 days] after D0 vaccination): Collection of SAEs and MAAEs

Review the MA and ask the subject or the subject's parent / guardian if the subject has experienced any SAEs since vaccination or any MAAEs since D30 (+14 days) visit.

- If an SAE has occurred, follow the instructions in Section 10 for reporting it.
- If an MAAE has occurred, follow the instructions in the Operating Guidelines.

Follow-up of subjects with Related AEs or with AEs That Led to Study/Vaccination Discontinuation:

Unless a subject or subject's parent/guardian refuses further contact, each subject who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the subject's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the product administered.
- The AE caused the discontinuation of the subject from the study or from vaccination.

5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ as, for example, the study will not start until all the appropriate regulatory and ethical approvals have been obtained

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject):	3 September 2019 to 12 October 2020
Planned inclusion period - FVFS to FVLS (first visit, last subject):	3 September 2019 to 02 March 2020
Planned end of study:	12 October 2020
Planned date of final clinical study report:	05 March 2021

Telephone call 2 (6-month follow up) of the last subject is considered to be the end of the study.

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Before the start of the trial, the Investigator or study staff may contact an appropriate pool of potential subjects and invite them to participate in the study. The site will ensure that any advertisements used to recruit subjects (eg, letters, pamphlets, posters) are submitted to Sanofi Pasteur prior to submission to the IEC/IRB for approval.

Subjects may be recruited from the site's patient database (ie, participants from studies MET50 or MET43) or the general population (only for Menveo vaccine-primed subjects to be assigned to Group 2, if applicable).

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject and/or a guardian voluntarily confirm his or her willingness to participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

In accordance with GCP, prior to signing and dating the consent form, the subject or guardian must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

If the subject or guardian is not able to read and sign the ICF, then it must be signed and dated by an impartial witness who is independent of the Investigator. A witness who signs and dates the consent form is certifying that the information in this form and any other written information had been accurately explained to and understood by the subject or guardian.

The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.

If new information becomes available that may be relevant to the subject or guardian willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

Informed consent forms will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy will be kept by the subject or the subject's guardian.

Documentation of the consent process should be recorded in the source documents.

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria to be eligible for study enrollment:

1. **Aged ≥ 13 to < 26 years** on the day of inclusion
2. Subject participated in and completed study MET50 (MET50 Groups 1, 2, or 3 only) or study MET43 (MET43 Groups 1, 2, or 3 only)
3. For MET59 Group 2 only (Menveo vaccine-primed subjects only; enrichment population): Subjects have a documented record of having received 1 dose of Menveo vaccine 3-6 years earlier either as part of a clinical trial or as routine vaccination. Subjects who participated in MET50 Group 4 can be enrolled if they fulfill this criterion
4. **Subject aged 13 to < 18 years**: assent form has been signed and dated by the subject and informed consent form (ICF) has been signed and dated by the parent or guardian
5. **Subjects aged ≥ 18 (or legal age of majority, if different from 18 years of age) to < 26 years**: ICF has been signed and dated by the subject
6. **Subject aged 13 to < 18 years**: both the subject and parent or guardian are able to attend all scheduled visits and to comply with all trial procedures
7. **Subjects aged ≥ 18 (or legal age of majority, if different from 18 years of age) to < 26 years**: able to attend all scheduled visits and to comply with all trial procedures

5.2.5 Exclusion Criteria

An individual fulfilling any of the following criteria is to be excluded from study enrollment:

1. Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 4 weeks after the last vaccination. To be considered of non-childbearing potential, a female must be pre-menarche, or post-menopausal for at least 1 year, or surgically sterile.
2. Participation in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
3. Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine before D30 except for influenza vaccination, which may be received at least 2 weeks before study investigational vaccine.

4. Receipt of immune globulins, blood or blood-derived products in the past 3 months
5. Receipt of any meningococcal vaccine including a licensed or investigational MenACWY vaccine or MenB vaccine since participation in study MET50 or MET43
6. Menveo vaccine-primed subjects only (enrichment group for Group 2): receipt of more than 1 dose of Menveo vaccine or vaccination with another licensed or investigational MenACWY vaccine or with a licensed or investigational MenB vaccine
7. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)
8. History of meningococcal infection, confirmed either clinically, serologically, or microbiologically.
9. At high risk for meningococcal infection during the trial (specifically but not limited to subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease)
10. Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances
11. Personal history of Guillain-Barré syndrome (GBS)
12. Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within at least 10 years of the proposed study vaccination
13. Verbal report of thrombocytopenia, contraindicating intramuscular vaccination
14. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination
15. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
16. Current alcohol abuse or drug addiction
17. Chronic illness (eg, HIV, hepatitis B, hepatitis C) that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion
18. Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided
19. Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
20. Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

If the subject has a primary physician who is not the Investigator, the site must contact this physician with the subject's / subject's parents' / guardians' consent to inform him / her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the subject is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the case report book (CRB). The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment

The reporting of signs and symptoms in lieu of a diagnosis is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and the information collected will not be coded. Its purpose is to assist in the later interpretation of safety data collected during the study.

5.2.7 Contraindications for Subsequent Vaccinations

An anaphylactic or other significant allergic reaction to the previous doses of one of the study vaccines.

Any contraindications for the subsequent MenB vaccinations will be referred to the Bexsero vaccine and Trumenba vaccine package inserts (32) (33).

5.2.7.1 Temporary Contraindications for Subsequent Blood Draw

- 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 indicated in the Tables of Study Procedures (5 to 7 days after vaccination at D0 for the D06 visit or 30 to 44 days after vaccination at D0 for the D30 visit).
- If postponement would result in the sample collection falling outside of the appropriate 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.

5.2.8 Conditions for Withdrawal

Subjects and/or the subjects' parents / guardians will be informed that they have the right to withdraw themselves or their child from the study at any time.

A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject's permission
- At the request of the subject (dropout)

The following will result in automatic withdrawal or exclusion of a subject from the study:

- Significant non-compliance with the protocol, on the basis of the Investigator's judgment

The reason for a withdrawal or dropout should be clearly documented in the source documents and in the CRB.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "Adverse Event") or for another reason.

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (ie, documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Study

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the CRB. Reasons are listed below from the most significant to the least significant (refer to the CRF completion instructions for additional details and examples):

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.3.2.1. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the Investigator and returned unsigned, and the subject or parent/guardian did not give any other news and did not come to any following visit.

Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is not an SAE or AE. • The subject or the parent/guardian signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit.
Withdrawal by Subject or Parent / Guardian / Legally Acceptable Representative	To be used: • When the subject or parent/guardian indicated unwillingness to continue in the study • When the subject or parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the study because of an AE or a protocol deviation.

For subjects where the reason for early termination was lost to follow-up or if the subject withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

If the subject's status at the end of the study is "Withdrawal by Subject or Parent / Guardian / Legally Acceptable Representative", the site will attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.2.12 Follow-up and Reporting of Pregnancies

Pregnancy is an exclusion criterion for enrollment in this study, but a subject could potentially become pregnant during her participation. In case of pregnancy during the primary series and if at least 1 dose of the study vaccine(s) has been administered, the subject will not be discontinued from the study, but no further vaccination will be administered until after delivery (if applicable and still within the study vaccination window). However, the subject will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

All pregnancy cases should be reported if they occurred during the study and during the 6 month follow-up period. To report the pregnancy case, the Investigator must fill out Pregnancy Reporting forms in the electronic data capture (EDC) system and inform the Sponsor within 1 month of identifying a pregnancy case.

If the EDC system is not available, the Investigator must fill out a paper Pregnancy Reporting Form (provided by the Sponsor at the start of the study) and inform the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome (ie, details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be provided to the Sponsor within 1 month of delivery.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, blighted ovum, fetal death, stillbirth, and congenital anomalies reported in the baby are always considered as SAEs, and the information should be provided to the Global Pharmacovigilance (GPV) Department regardless of when the SAE occurs (eg, even after the end of the study).

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on how to address any study related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to GPV Department (Please refer to Section 10).

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.4.

5.4 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (eg, those that affect the conduct of the study or the safety of subjects) require IEC / IRB approval, and must also be forwarded to regulatory authorities.

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs / IRBs should only be notified, no formal approval is required.

The Investigator is responsible for ensuring that changes to an approved study, during the period for which IEC / IRB approval has already been given, are not initiated without IEC / IRB review and approval, except to eliminate apparent immediate hazards to subjects.

5.5 Interruption of the Study

The study may be discontinued if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the country where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by applicable regulatory requirements. The Investigator shall promptly inform the study subjects / subjects' parents/guardians and assure appropriate subject therapy and/or follow-up for them.

There will be an internal team at the level of the Sponsor (Safety Management Team, [SMT]), which will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in both recruitment and / or further vaccination while it investigates any potential signal or concern.

6 Products Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product

MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)

Form: Liquid solution

Dose: 0.5 milliliter (mL)

Route: IM

Batch number: To be determined

6.1.1.1 Composition

Each 0.5 mL dose of MenACYW conjugate vaccine contains the following components:

Meningococcal capsular polysaccharides:

Serogroup A ..... 10 µg
Serogroup C ..... 10 µg
Serogroup Y ..... 10 µg
Serogroup W ..... 10 µg

Tetanus toxoid protein carrier ..... approximately 55 µg[a]

6.1.1.2 Preparation and Administration

MenACYW conjugate vaccine is supplied in single-dose (0.5 mL) vials.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor.

The rubber stopper should not be removed from any of the vaccine vials.

One dose (0.5 mL) of MenACYW will be administered IM (in the deltoid muscle of the arm). The site of injection should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle will be disposed of in accordance with currently established guidelines.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

All subjects will receive 1 dose of MenACYW conjugate vaccine on D0.

6.1.2 Identity of Control Products

Not applicable.

6.2 Identity of Other Products

6.2.1 Other Product 1

Trumenba vaccine: Meningococcal Group B Vaccine (Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc, Philadelphia, PA, USA)

Form: Liquid solution

[a]Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide -to-protein ratio for the conjugates used in each formulation.

Dose: 0.5 milliliter (mL)

Route: IM

Batch number: To be determined

6.2.1.1 Composition

Liquid suspension

Each 0.5 mL dose of vaccine contains recombinant lipidated factor H binding protein (fHBP) variants from *Neisseria meningitidis* (*N meningitidis*) group B:

fHBP subfamily A	60 µg
fHBP subfamily B	60 µg
PS80	0.018 mg
Al^{3+} as AlPO4 in histidine buffered saline	0.25 mg

6.2.1.2 Preparation and Administration

The procedures for administering Trumenba vaccine are the same as those described for the study product in Section 6.1.1.2, with Trumenba vaccine to be given by IM injection in the contralateral arm (ie, the opposite to that which the MenACYW conjugate vaccine is administered).

Also see Trumenba vaccine package insert (32).

6.2.1.3 Dose Selection and Timing

All subjects in Group 3 will receive 1 dose of Trumenba vaccine on D0.
Note: The 2nd dose of Trumenba vaccine should be given at the D30 visit after completion of study procedures, and a 3rd dose [or 2nd dose, if the alternate 2-dose schedule is used instead by the study Investigators] will be given at D180. The first dose of the vaccine will be provided by the Sponsor. Subsequent doses needed to complete the vaccination series will be procured by the sites and reimbursed by the Sponsor.

6.2.2 Other Product 2

Bexsero vaccine: Meningococcal group B Vaccine (recombinant deoxyribonucleic acid [rDNA], component, adsorbed) (GSK Vaccines, Srl, Sovicille (SI), Italy)

Form: Liquid solution

Dose: 0.5 milliliter (mL)

Route: IM

Batch number: To be determined

6.2.2.1 Composition

A Bexsero vaccine suspension for injection is supplied in pre-filled syringe.

Each 0.5 mL dose contains:

Recombinant N meningitidis group B NHBA fusion protein [1, 2, 3]	50 µg
Recombinant N meningitidis group B NadA protein [1, 2, 3]	50 µg
Recombinant N meningitidis group B fHbp fusion protein [1, 2, 3]	50 µg
Outer membrane vesicles from N meningitidis group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4[2]	25 µg

[1] Produced in *E coli* cells by recombinant DNA technology
[2] Adsorbed on aluminum hydroxide (0.5 mg Al3+)
[3] NHBA (Neisseria Heparin Binding Antigen), NadA (Neisseria adhesin A), fHbp (factor H binding protein).
The vaccine contains the following excipients: sodium chloride, histidine, sucrose, water for injections.

6.2.2.2 Preparation and Administration

The procedures for administering Bexsero vaccine are the same as those described for the study product in Section 6.1.1.2, with Bexsero vaccine to be given by IM injection in the contralateral arm (ie, the opposite to that which the MenACYW conjugate vaccine is administered).

Also see Bexsero vaccine package insert (33).

6.2.2.3 Dose Selection and Timing

All subjects in Group 4 will receive 1 dose of Bexsero vaccine on D0.
Note: A 2nd dose of Bexsero vaccine should be given at the D30 visit after completion of study procedures. The first dose of the vaccine will be provided by the Sponsor. Subsequent doses needed to complete the vaccination series will be procured by the sites and reimbursed by the Sponsor.

6.3 Product Logistics

6.3.1 Labeling and Packaging

The investigational product, MenACYW conjugate vaccine (single-dose vials), will be supplied with investigational labeling and packaging according to national regulations and will not be blinded. Each single dose of investigational product will be identified by a unique number on the detachable label and on the outer carton label. The carton label will also have a detachable label for the sites to attach to the source documents. See the Operating Guidelines for additional label details.

The concomitant products are not blinded and will retain original commercial labeling and packaging with no additional labels applied.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Clinical Logistics Coordinator or designee will contact the Investigator or a designee to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (ie, verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this responsibility.

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The vaccines must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the trial site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.3.2.3 Product Accountability

The person in charge of product management at the site will maintain records of product delivery to the trial site, product inventory at the site, the dose(s) given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the CRF. If applicable, information may also be entered into the subject's vaccination card.

The Sponsor's monitoring staff will verify the trial site's product accountability records against the record of administered doses in the CRBs and the communication from the IRT (if applicable).

In case of any expected or potential shortage of product during the trial, the Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

6.3.3 Replacement Doses

If a replacement dose is required (eg, because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

Unused or wasted products will be returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the study period.

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigator(s) will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

MET59 is an open-label study; therefore, there is no need for code-breaking procedures.

Until database lock and to prevent biases, the laboratory personnel performing the serology testing will be blinded to the group assignment. The laboratory will have a written procedure detailing how the blinding will be maintained.

6.5 Randomization and Allocation Procedures

MenACYW conjugate vaccine-primed subjects (from either MET50 or MET43) will be randomized in a 2:1:1 ratio to receive a booster dose of MenACYW conjugate vaccine alone (Group 1, 200 subjects) or to receive a booster dose of MenACYW conjugate vaccine concomitantly with licensed MenB vaccines (Trumenba vaccine; Group 3, 100 subjects, or Bexsero vaccine; Group 4, 100 subjects). Subjects primed with Menveo vaccine in MET50 or outside of Sanofi Pasteur trials will be assigned to Group 2 (200 subjects, which will not be randomized).

All subjects primed with MenACYW conjugate vaccine who meet the inclusion / exclusion criteria will be randomly assigned to Group 1, 3, or 4 in a 2:1:1 ratio, while subjects primed with Menveo vaccine will be automatically allocated to Group 2 (not randomized).

Site staff will call the IRT, enter identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then state the vaccine dose assignment and whether the subject has been assigned to the D06 blood-draw subset. The full detailed procedures for randomization are described in the Operating Guidelines. If the subject is not eligible to participate in the trial, then the information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example,

Subject 840000100005 is the fifth subject enrolled in Center Number 1 in the US (840 being the US country code).

Subject numbers should not be reassigned for any reason. The Research and Development (R&D) Site Quality Operations Department at Sanofi Pasteur will hold the randomization codes in a secured location.

6.6 Treatment Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified study personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the study site, product inventory at the site, dose(s) given to each subject, and the disposal of unused or wasted doses

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications including but not limited to other therapies (eg, blood products), should be recorded in the source documents. All new medications prescribed for new medical conditions / AEs during study participation should also be recorded in the source documents.

Documentation in the CRB of concomitant medication(s) will be limited to specific categories of medication(s) (Categories 1, 2, and 3 as detailed below). Those will include Category 1, 2, and 3 medications ongoing at the time of inclusion in the study, or started at any time during the subject's participation in the trial. For category 3 medication, the period of reporting in CRB will be restricted to only 3 days (72 hours) prior to each blood sampling time point.

Collection period in source documents

Reportable medications (Category 1, 2, and 3) will be collected in the source documents from the day of first vaccination to the end of the trial.[a]

Categories of Reportable medications and reporting period

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination.

1) Category 1: Reportable medications with potential impact on the evaluation of the safety of the study vaccines. For example, antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids (therapy duration less than 2 weeks), and other immune modulators.

[a] Subjects/ Subject's parents will be required to document all medications received in the Diary Cards. The sites will focus on only recording the medications belonging to the 3 categories in the other source documents.

Note: Topical steroids (Inhaled, otic, ophthalmic, nasal etc.) should not be captured or reported.

- Category 1 medications will be reported in the CRB from the day of first vaccination to the end of the solicited and unsolicited follow-up period after each vaccination. These medications will also be collected in the CRB for the 30- day period prior to the subsequent doses of the vaccine, wherever applicable (second, third, fourth, etc., in case of a multi-dose schedule with more than a 30-day interval between doses).

2) Category 2: Reportable medications with potential impact on immune response of the study vaccines and used to define the Per-Protocol Analysis Set (PPAS). For example:

- Influenza and other non-study vaccines: Influenza vaccine in the 2 weeks (14 days) preceding the trial vaccination up to the last blood draw and any other vaccines (other than the study vaccine) in the 4 weeks preceding the trial vaccination up to the last blood draw
- Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
- Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) within past 3 months, anti-cancer chemotherapy, anti-proliferative drugs such as DNA synthesis inhibitors, or radiation therapy: used in the 6 months preceding the first trial vaccination, and up to the last blood draw.
    - Category 2 medications will be reported in the CRB according to the collection period detailed above up to the last blood draw.

3) Category 3: Systemic (Oral or injectable) antibiotics, as they may interfere with bioassays used for antibody testing when taken before a blood draw.

- Category 3 medications will be reported in the CRB for the period of 3 days (72 hours) before each blood draw.

Note: Topical antibiotics (Inhaled, otic, ophthalmic, nasal, etc.) should not be captured or reported.

The information reported in the CRB for each reported medication will be limited to:

- Trade name
- Rationale for the origin of prescription: Whether it was a prophylactic[a]* medication? Prophylactic medications will be recorded in the Action Taken section of the AE collection tables.
- Medication category (1, 2, or 3)
- Start and stop dates

[a] Medication(s) prescribed for preventing AE occurrence (e.g. paracetamol to reduce the risk of fever)

Dosage and administration route, homeopathic medication, will not be recorded.

If the subject has received medications other than those listed in Categories 1, 2, and 3, the detailed information will be collected in the source documents only.

Medications given to treat an AE will be captured in the "Action Taken" section of the AE CRB only. No details will be recorded in the concomitant medication CRB unless the medication(s) received belongs to one of the prelisted categories.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at D0, D06, and D30. See the Tables of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At the D0, D06 and D30 visits, 20 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label, and will attach the label to the tube. When vaccination and blood sample collection occur at the same visit and vaccine is given only in one of the arms, blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of antibody response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours in order to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C after the period of clotting at room temperature and must be centrifuged within a maximum of 24 hours.

The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes. These tubes are pre-labeled with adhesive labels that identify the study code, the subject's number and the sampling site or visit number.

The subject's number and the date of sampling, the number of aliquots obtained, the date and time of preparation, and the subject's consent for future use of his / her samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

7.3 Sample Storage and Shipment

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented on the appropriate form during the entire study. If it rises above -10°C for any period of time, the Clinical Logistics Coordinator must be notified. See the Operating Guidelines for further details.

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to GCI at Sanofi Pasteur. The address is provided in the Operating Guidelines.

Any unused part of the serum samples will be securely stored for any testing directly related to this study at the Sanofi Pasteur serology laboratory (GCI) for up to 25 years after the end of the study.

7.4 Future Use of Stored Serum Samples for Research

Subjects or subjects' parent/guardians will be asked to indicate in the ICF whether they will permit the future use of any leftover stored serum samples for additional research not related to this study. If they consent, leftover serum samples will be securely stored at GCI for up to 25 years after the end of the study. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, diary cards, memory aids, and other study documents, as well as with the following study materials: all study vaccines, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

The means for performing Electronic Data Capture (EDC) will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the study.

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and / or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent

countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and for the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

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

9.1.1.2 Immunogenicity Assessment Methods

Antibodies to Meningococcal Antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in an 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.

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 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 vaccines (Groups 3 and 4)

9.2.1.2 Immunogenicity Assessment Methods

The immunogenicity assessment method for the secondary endpoints for hSBA is the same as that presented in Section 9.1.1.2.

9.2.2 Safety

There are no secondary objectives for safety.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 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)

9.3.1.2 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 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.

9.3.2 Safety

9.3.2.1 Safety Definitions

The following definitions are taken from the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

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

Adverse Event (AE):

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 serious 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 (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious* which is based on subject / event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability / incapacity[c]
- Is a congenital anomaly / birth defect
- Is an important medical event (IME)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new-onset diabetes, or autoimmune disease.

Adverse Reaction:

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

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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.

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.

The assessment of these reactions by the Investigator is mandatory.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if 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 D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Medically-Attended Adverse Events (MAAE):

An MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject or subject's parent/guardian to seek unplanned medical advice at a health care provider's office or Emergency Department. This definition excludes pre-planned medical office visits for routine pediatric check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. Health care provider contact made over the phone or by email will be considered a physician office visit for the purpose of MAAE collection. The outcome of the health care provider contact (whether it results in a prescription or not) will not be considered as a basis for reporting the event as an MAAE and all contacts should be reported. Sufficient data should be collected for the event to allow an assessment of the causality and diagnosis, if possible.

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

An AESI is an event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done.

Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

9.3.2.2 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 case report book [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

9.3.2.3 Safety Assessment Methods

At the D30 visit, the Investigator or a delegate will ask the subject or the subject's 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.

9.3.2.3.1 Immediate Post-Vaccination Surveillance 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 Section 10.

9.3.2.3.2 Reactogenicity (Solicited Reactions from Day 0 to Day 7 after Vaccinations)

After vaccination, subjects or the subject's parents / guardians will be provided with a diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects or the subject's 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 subject / parent or guardian to treat and/or manage any **solicited reactions** will be classified in the CRB using the following list (all applicable items should be checked):

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

Subjects or the subject's 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 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 9.1 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 / legally acceptable representatives 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 9.2 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 / legally acceptable representatives 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 subject's parents / guardians are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRB. The preferred route for this trial is oral. Pre-vaccination temperature is also systematically collected by the Investigator in the source document. Tympanic thermometers must not be used.

9.3.2.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, subjects / parents / guardians 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 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 Section 10 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 9.1 and Table 9.2).

All other unsolicited AEs will be classified according to the following 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.

[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 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
- 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 9.3.2.7.

- Action taken for each AE (eg, medication)

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

9.3.2.4 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 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 Section 10.4.

See Section 10 for further details on SAE reporting.

9.3.2.5 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 9.3.2.6.

9.3.2.6 Adverse Events of Special Interest

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

- Generalized seizures (febrile and non-febrile) (40) (41)
- Kawasaki disease (42) (43)
- Guillain-Barré syndrome (44)
- Idiopathic thrombocytopenic purpura (ITP) (45) (46)

These events have been listed as AESIs on the basis of the feedback received from the EU 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 Section 10. Further instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

9.3.2.7 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.

9.3.3 Efficacy

No clinical efficacy data will be obtained in the study.

10 Reporting of Serious Adverse Events

To comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship, and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product(s). It is the responsibility of the Investigator to request all necessary documentation (eg, medical records, discharge summary) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

Serious adverse events occurring during a subject's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The Investigator (licensed physician [M.D. or D.O.]) must validate the information entered on the AE CRF by completing the Investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form as well as the appropriate Safety Complementary Information CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the RMO with relevant SAE information details.

If the EDC system is unavailable, the site must notify the Sponsor, using the paper version of the CRB, as described in the operating guidelines.

The Investigator must complete the paper copies of the AE CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by any of the following means:

- By fax, to the following number: 570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com (see the Operating Guidelines for directions on how to send a password-protected email).
- By express mail, to the following address:

  Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global Pharmacovigilance

Mail Drop: 45D38
Discovery Drive
Swiftwater, PA 18370

When the EDC system becomes available, the Investigator must transcribe the information from the paper forms into the EDC system.

If there is need for urgent consultation, the Investigator is to contact the RMO. If the RMO cannot be reached, the Investigator may contact the Call Center as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (eg, outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the AE CRF and the appropriate Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPV Department and to the CRA. Copies of documents (eg, medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the subject must always be respected when forwarding this information.

10.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Any SAE that occurs after a subject has completed the study but that is likely to be related to the investigational product(s), other products (eg, a benefit vaccine), or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.3.2.7.

Following this, the Sponsor's Global Safety Officer will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The causal relationship to study procedures will be also assessed in the CRB.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigators.

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

The Sponsor's RMO, [redacted] will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the study protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information. These diary cards will include prelisted terms and intensity scales (see Table 9.1and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Subjects / parents or guardians will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects / parents or guardians on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects either during a visit or over the telephone using a questionnaire to capture SAEs and AESIs, if applicable. A memory aid may be provided to the subjects at the preceding study visit to help them record information on events occurring between this visit and the 6-month follow-up.

Relevant information will be transcribed into the AE CRF. Any SAEs captured during this 6-month follow-up period will be reported and followed-up as per the normal process for reporting SAEs.

At specified intervals, the Investigator or an authorized designee will interview the subjects / parents or guardians to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRBs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in study personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any study personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry to track all modifications and ensure database integrity.

The Investigator is responsible for the timeliness, completeness, and accuracy of the information in the CRBs; must provide explanations for all missing information; and must sign the CRB using an e-signature.

11.2 Data Management

Management of SAE Data and Pregnancy Data

During the study, SAE data (reported on the AE and Safety Complementary Information CRFs) and pregnancy data (reported by the Investigator on ePregnancy Forms) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the Global Safety Officer and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information from the GPV database cases will be reconciled with that in the clinical database

Management of Clinical and Laboratory Data

Clinical data, defined as all data reported in the CRB, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.

During the study, clinical data reported in the CRBs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and / or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical data will be submitted to the Investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

The validation of the immunogenicity data will be performed at the laboratory level following the laboratory's procedures. Information from the laboratory will be checked for consistency before integration into the clinical Data warehouse.

After integration of all corrections in the complete set of data, and after the SAE information available from CDM and the GPV Department has been reconciled, the database will be released for statistical analysis.

11.3 Data Review

Review of the data is anticipated through the data review process led by Data Management before database lock.

The safety of the investigational product will be continuously monitored by the Sponsor. Periodic safety data reviews will be performed by the Sponsor's Safety Management Team (SMT).

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Clinical data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor. A statistical analysis plan (SAP) will be written and peer reviewed before any analyses. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

All immunogenicity analyses will be performed on the Per-Protocol Analysis Sets (PPAS1 for D06 and PPAS2 for D30). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set. All safety analyses will be performed on the Safety Analysis Set.

12.1.1 Hypotheses and Statistical Methods for Primary Objectives

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% confidence interval (CI) calculated using the exact method (Clopper-Pearson method) for percentage of subjects with hSBA seroresponse against serogroups A, C, W and Y 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, W and Y. The CI for the single proportion will be calculated using the exact method (Clopper-Pearson method).

*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.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

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

12.1.2.1 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.

12.1.2.2 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.

12.1.2.3 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.

12.1.2.4 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.

12.1.2.5 Secondary Objective 5

Thirty days after the administration of MenACYW conjugate vaccine when administered alone or concomitantly with Trumenba vaccine or Bexsero vaccine vaccines, 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 4, and between Group 1 and pooled Groups 3 and 4 will be calculated, and 95% CI will be provided.

12.1.3 Hypotheses and Statistical Methods for Observational Objectives

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

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 from 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.

Additional subgroup analyses of the hSBA vaccine seroresponse rates, hSBA titer ≥ 1:4 and ≥ 1:8, hSBA GMTs, rSBA vaccine seroresponse rates, rSBA titer ≥ 1:8 and ≥ 1:128, and rSBA GMTs will also be provided by number of years (3 years, 4 years, 5 years, and 6 years) 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).

Safety

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

1. The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions occurring from D0 to D07 after each vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken. Since MenACYW conjugate vaccine and the concomitant MenB vaccines will be administered in different limbs, solicited injection site reactions can be distinguished between the two products, and will be analyzed and presented separately.
2. Immediate unsolicited systemic AEs and unsolicited AEs occurring up to D30 after each vaccination will be summarized.
3. The number and percentage of subjects reporting any unsolicited non-serious AEs will be summarized by study group, intensity, time of onset period, duration, and by MedDRA preferred term and system organ class (SOC), as well as by relationship to the study vaccine.
4. The number and percentage of subjects reporting at least one of any MAAEs will be summarized throughout the trial.
5. The number and percentage of subjects reporting at least one of any SAEs will be summarized by study group, seriousness criterion, outcome, and by MedDRA preferred term and SOC, as well as by relationship to the study vaccine.
6. The number and percentage of subjects reporting at least one of any AESIs will be summarized throughout the trial.
7. Exact (Clopper-Pearson) 2-sided 95% CIs will be calculated for the percentages.

Additional subgroup safety analyses will also be provided by number of years (3 years, 4 years, 5 years, and 6 years) 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).

12.2 Analysis Sets

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

12.2.1 Full Analysis Set

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 FAS 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.

12.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one 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).

12.2.3 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. Two PPAS will be defined (PPAS1 for D06 and PPAS2 for D30). The subjects presenting with at least one 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 one 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).

12.2.4 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. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized or assigned.

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

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

12.3 Handling of Missing Data and Outliers

12.3.1 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 ≥ upper limit of quantitation [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

12.3.2 Safety

No replacement will be done.

12.3.3 Efficacy

Not applicable.

12.4 Interim / Preliminary Analysis

No analyses are planned.

12.5 Determination of Sample Size and Power Calculation

12.5.1 Calculation of Sample Size

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.

12.5.2 Power Calculations 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 12.1 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.

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Trial / Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and / or national regulations and directives.

13.2 Source Data and Source Documents

“Source data” are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a diary card, the study coordinator will obtain verbal clarification from the subject, enter the response into the "Investigator's comment" page of the diary card, and transfer the information to the CRB.

The subject pre-screening log should list all individuals contacted by the Investigators to participate in the trial, regardless of the outcome.

The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

Good Documentation Practice should be followed by the Investigator and the site staff managing source documents.

13.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a subject's medical records are not at the investigational site, it is the responsibility of the investigator to obtain those records if needed.

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the General Data Protection Regulation. Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subjects' race and ethnicity will be collected in this study because these data are required by the Food and Drug Administration in the US (47).

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

[a] Unless the electronic medical records are managed by validated computerized systems that are compliant with US 21 CFR Part 11, in which case they are acceptable on their own.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the trial (ie, before the inclusion of the first subject at the first center the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the site; and that the study Investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study Investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the CRF Completion Instructions for entering data into the CRB, and the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

After the start of the study, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits, and must allow the Sponsor/delegate staff direct access to subject medical files and CRBs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (eg, protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.

After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the study, a close-out visit will be performed to ensure that:

- The center has all the documents necessary for archiving
- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical Quality Assessment department (CQA) or by independent auditors to verify that the study has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to study documents during these inspections and audits.

13.4.3 Archiving

The Investigator and the study site shall retain and preserve 1 copy of the study file containing the essential documents related to the study and records generated during the study ("Study File") for the longer of the 2 following periods ("Retention Period"):

- 25 years after the signature of the final study report or
- such longer period as required by applicable regulatory requirements

If during the Retention Period, the study site is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), the study site shall contact the Sponsor to organize the transfer of the Study File to the Sponsor's designee at the Sponsor's expense. Following the Retention Period, the Investigator and/or the study site are responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the study will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A Clinical Trial Agreement will be signed by all the parties involved in the study's performance, if relevant. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and / or the study protocol.

13.6 Stipends for Participation

Subjects and / or the subject's parent / guardian may be provided with a stipend according to local practice to compensate for the time and travel required for study visits and procedures.

13.7 Publication Policy

Data derived from this trial are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the trial must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the trial, any participating center may publish or otherwise use its own data provided that any publication of data from the trial gives recognition to the trial group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

Sanofi Pasteur must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this trial at least 90 days prior to submission for publication / presentation. Any information identified by Sanofi Pasteur as confidential must be deleted prior to submission, it being understood that the results of this trial are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

14 Reference List

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