NCT04142242

Safety and Immunogenicity of a Single Dose of MenACYW Conjugate Vaccine at Least 3 Years Following Initial Vaccination With Either Menomune® Vaccine or MenACYW Conjugate Vaccine in Older Adults

Phase III, randomized, open-label, multi-center study to evaluate the safety and immunogenicity of a single dose of MenACYW conjugate vaccine in subjects who received a dose of Menomune® vaccine or MenACYW conjugate vaccine ≥ 3 years previously, at ≥ 56 years of age. Antibody persistence following the primary dose of either Menomune vaccine or MenACYW conjugate vaccine will also be evaluated.

Clinical Study Protocol, Amendment 2

Health Authority File Number:	BB-IND #: 14171
WHO Universal Trial Number (UTN):	U1111-1217-2058
Study Code:	MEQ00066
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form/Route:	Liquid Solution/Intramuscular (IM)
Indication For This Study:	Single dose of MenACYW conjugate vaccine for adults ≥ 56 years of age 3 years after the primary dose
Manufacturer:	Same as Sponsor
Coordinating Investigator:	To be determined
Sponsor's Responsible Medical Officer:	[redacted]
Pharmacovigilance Global Safety Expert:	Global Pharmacovigilance & Epidemiology, Sanofi Pasteur Inc.
Clinical Trial Manager:	[redacted]
Version and Date of the Protocol:	Version 3.0 dated 11 September 2020

History of Protocol Versions

Version*	Date	Comments
1.0	24 April 2019	First version used in the study
2.0	09 April 2020	Protocol Amendment 1

* Version in bold font has 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: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Active Substances:	Capsular polysaccharide from meningococcal serogroups A, C, W, and Y conjugated to tetanus toxoid

Title of the Study:	Safety and Immunogenicity of a Single Dose of MenACYW Conjugate Vaccine At Least 3 Years Following Initial Vaccination With Either Menomune Vaccine or MenACYW Conjugate Vaccine in Older Adults
Development Phase:	Phase III
Coordinating Investigator:	To be determined
Study Sites:	This study will be conducted in 34 centers in in the United States. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Q3 2019 to Q1 2022
Study Design, Schedule of Study Procedures, and Methodology:	This will be a Phase III, 2-stage, randomized, open-label, multi-center study to evaluate the safety and immunogenicity of a single dose of MenACYW conjugate vaccine ≥ 3 years after a prior dose of either Menomune® vaccine or MenACYW conjugate vaccine in subjects ≥ 56 years of age at the time of primary vaccination. Antibody persistence after primary vaccination with Menomune vaccine or MenACYW conjugate vaccine will also be evaluated. The study will be conducted in 2 stages. Subjects who received Menomune vaccine or MenACYW conjugate vaccine in Study MET49 or Study MET44 are eligible for enrollment in Study MEQ00066. A planned minimum of 440 subjects who participated in Study MET49 (i.e., 3 years prior to enrollment in the current study) will be randomly assigned to Group 1 or Group 3, or Group 2 or Group 4, depending on the vaccine originally received in Study MET49. These subjects will have antibody persistence assessed, followed by receipt of a single dose of MenACYW conjugate vaccine as per the stages described below. ***Stage I:*** Group 1: Approximately 180 subjects who received Menomune vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 (to assess antibody persistence 3 years after primary vaccination), followed by receipt of a single dose of MenACYW conjugate vaccine (ratio 9:2 [Group 1:Group 3]). The first 60 subjects enrolled in Group 1 will comprise a subset from which an additional blood sample will be obtained at 6 (window, 5–7) days post-vaccination. Group 2: Approximately180 subjects who received MenACYW conjugate vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 (to assess antibody persistence 3 years after primary vaccination), followed by receipt of a single dose of MenACYW conjugate vaccine

	(ratio 9:2 [Group 2:Group 4]). The first 60 subjects enrolled in Group 2 will comprise a subset from which an additional blood sample will be obtained at 6 (window, 5–7) days post-vaccination. Group 3: Approximately 40 subjects who received Menomune vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 for the assessment of antibody persistence 3 years after primary vaccination. Group 4: Approximately 40 subjects who received MenACYW conjugate vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 for the assessment of antibody persistence 3 years after primary vaccination. A planned total of 120 subjects who participated in Study MET44 (i.e., 6–7 years prior to enrollment in the current study) will provide a blood sample at enrollment in Study MEQ00066 for the assessment of antibody persistence 6–7 years after primary vaccination with either Menomune vaccine or MenACYW conjugate vaccine. These subjects will not receive a vaccination with MenACYW conjugate vaccine at enrollment. The subjects will be grouped as follows: Group 5: 60 subjects who received Menomune vaccine in Study MET44 Group 6: 60 subjects who received MenACYW conjugate vaccine in Study MET44 ***Stage II (2 years after enrollment)*** Group 3: The approximately 40 subjects who were randomly assigned to this group at the time of initial enrollment in Study MEQ00066 will provide an additional blood sample (to assess antibody persistence at 5 years), followed by receipt of a single dose MenACYW conjugate vaccine. Group 4: The approximately 40 subjects who were randomly assigned to this group at the time of initial enrollment in Study MEQ00066 will provide an additional blood sample (to assess antibody persistence at 5 years), followed by receipt of a single dose of MenACYW conjugate vaccine. **Immunogenicity** ***Stage I*** All subjects (Groups 1–6) will provide a blood sample at enrollment (Visit 1) to be tested for antibody persistence 3 years (Groups 1–4) or 6–7 years (Groups 5 and 6) after having received primary vaccination in Study MET49 or Study MET44, respectively. Subjects in Group 1 and Group 2 will receive a single dose of MenACYW conjugate vaccine and will provide a blood sample 30 (window, + 14) days later. A subset of subjects, approximately 60 in Group 1 and 60 in Group 2, will also provide a blood sample 6 (window, 5–7) days following vaccination. Subjects in Groups 3 and 4 will not receive vaccination during Stage I. These subjects will continue into Stage II of the study (see below). Subjects in Groups 5 and 6 will provide a blood sample at the time of enrollment in Study MEQ000666 to assess for antibody persistence 6–7 years after primary vaccination with Menomune vaccine or MenACYW

	conjugate vaccine. Subjects in Groups 5 and 6 will not receive vaccination, and no further follow-up is planned for these groups. It is possible that some subjects in Groups 5 and 6 may have serum bactericidal assay using human complement (hSBA) titers < 1:8 (the putative level of protection against invasive meningococcal disease) to 1 or more vaccine serogroups (A, C, W, or Y). Investigators will be informed of and notify all subjects in Groups 5 and 6 whose hSBA titers are < 1:8. Regardless of group assignment, it is possible that some subjects may have antitetanus antibody titers < 0.1 IU/mL (the putative level of protection against tetanus disease). Investigators will be informed of and notify all subjects whose antitetanus antibody titers are < 0.1 IU/mL. ***Stage II*** Two years after enrollment in Study MEQ00066 (i.e., approximately 5 years after primary vaccination in Study MET49), subjects in Groups 3 and 4 will provide a blood sample for assessment of antibody persistence, followed by receipt of a single dose of MenACYW conjugate vaccine, and a post-vaccination blood sample 30 days later. **Safety** ***Stages I and II*** Subjects who are revaccinated with MenACYW conjugate vaccine (i.e., subjects in Groups 1 and 2 during Stage I, and subjects in Groups 3 and 4 during Stage II) will record information about solicited reactions from Day 0 through Day 7 after vaccination. Information on unsolicited adverse events (AEs), including medically attended adverse events (MAAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs), will be collected from Day 0 through ~Day 30 after vaccination. For Groups 3 and 4 after Visit 1 and 5 and 6, only SAEs considered by the Investigator to be related to study procedures (e.g., blood sampling) will be collected.
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 that warrant study discontinuation; or for administrative reasons; or on advice of the Sponsor, the Investigators, the Institutional Review Boards (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 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 Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	To demonstrate sufficiency of the vaccine seroresponse to meningococcal serogroups A, C, W, and Y following administration of a single dose of MenACYW conjugate vaccine to Group 1 subjects (who received primary vaccination with Menomune vaccine ≥ 3 years earlier at ≥ 56 years of age in Study MET49).
Primary Endpoint:	Vaccine seroresponse to meningococcal serogroups A, C, W, and Y as measured by hSBA at baseline (D0, pre-vaccination) and 30 (window, +14) days after vaccination in Group 1 (Menomune-primed) subjects.

Secondary Objectives:	Secondary Objective 1 • To demonstrate sufficiency of the vaccine seroresponse to meningococcal serogroups A, C, W, and Y following administration of a single dose of MenACYW conjugate vaccine to Group 2 subjects (who received primary vaccination with MenACYW conjugate vaccine ≥ 3 years earlier at ≥ 56 years of age in Study MET49). Secondary Objective 2 • To describe vaccine seroresponse rates with respect to serogroups A, C, W, and Y in serum specimens collected 6 (window, 5–7) days post-vaccination in approximately 60 subjects from Group 1 (Menomune-primed) and approximately 60 subjects from Group 2 (MenACYW conjugate vaccine-primed). Secondary Objective 3 • To describe antibody persistence ≥ 3 years after primary vaccination with Menomune vaccine or MenACYW conjugate vaccine for subjects from all groups.
Secondary Endpoints:	• Vaccine seroresponse to meningococcal serogroups A, C, W, and Y as measured by hSBA at baseline (D0, pre-vaccination) and 30 (window, +14) days after vaccination in Group 2 (MenACYW conjugate vaccine-primed) subjects. • Vaccine seroresponse 6 (window, 5–7) days after vaccination as measured by hSBA in approximately 60 subjects from Group 1 and approximately 60 subjects from Group 2. • During Stage I, antibody persistence after primary vaccination with Menomune vaccine or MenACYW conjugate vaccine as measured by hSBA and serum bactericidal assay using baby rabbit complement (rSBA) will be evaluated at Day 0 in Groups 1-4 (3 years after primary vaccination in Study MET49) and in Groups 5 and 6 (6-7 years after primary vaccination in Study MET44). Two years later, during Stage II, antibody persistence will be evaluated again in Groups 3 and 4 (5 years after primary vaccination in Study MET49).
Observational Objectives:	***Immunogenicity*** • To describe the immunogenicity of a single dose of MenACYW conjugate vaccine, as assessed by hSBA and rSBA antibody titers, among persons who previously received Menomune vaccine or MenACYW conjugate vaccine ≥ 3 years earlier. • To describe antibody levels against tetanus toxoid at enrollment (all groups), 2 years after enrollment (Groups 3 and 4), and 30 (window, + 14) days after a single dose of MenACYW conjugate vaccine (Groups 1–4) in Study MEQ00066. ***Safety*** To describe the safety profile of a single dose of MenACYW conjugate vaccine administered to adults who received Menomune vaccine or MenACYW conjugate vaccine ≥ 3 years earlier (Groups 1 and 2 during Stage I; Groups 3 and 4 during Stage II).

Observational Endpoints:	***Immunogenicity*** Antibody titers (hSBA and rSBA) will be measured for each meningococcal serogroup for the following groups of subjects: • For all subjects on Day 0 • For a subset of subjects in Groups 1 and 2, on Day 6 (window, Days 5–7) following vaccination • For subjects in Group 3 and 4, on Day 0 + 2 years • For all subjects who receive a single dose of MenACYW conjugate vaccine, 30 (window, + 14) days following vaccination Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested to assess: • Antibody concentrations against tetanus toxoid at Day 0 (all groups), 2 years after enrollment (Groups 3 and 4), and 30 (window, + 14) days after the administration of a single dose of MenACYW conjugate vaccine in Study MEQ00066 (Groups 1–4) ***Safety*** • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination. • Occurrence, time to 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 from Day 0 through Day 7 after vaccination. • Occurrence, time to 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 from Day 0 through Day 7 after vaccination. • Occurrence, nature (MedDRA preferred term), time to 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 occurring from Day 0 through ~Day 30 after vaccination. MAAEs will be collected as unsolicited non-serious AEs from Day 0 through ~Day 30 after vaccination. • Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs, including AESIs, throughout the study.
Planned Sample Size:	A total of 560 subjects are planned to be enrolled: • Group 1 (subjects who received Menomune vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine at enrollment in Study MEQ00066: n=180 • Group 2 (subjects who received MenACYW conjugate vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine at enrollment in Study MEQ00066: n=180

	• Group 3 (subjects who received Menomune vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine 2 years after enrollment in Study MEQ00066: n=40 • Group 4 (subjects who received MenACYW conjugate vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine 2 years after enrollment in Study MEQ00066: n =40 • Group 5 (subjects who previously received Menomune vaccine in Study MET44): n=60 • Group 6 (subjects who previously received MenACYW conjugate vaccine in Study MET44): n=60
Duration of Participation in the Study:	The duration of active participation in the study will be 30 (window, + 14) days for subjects in Groups 1 and 2; 2 years plus 30 (window, + 14) days for Groups 3 and 4; and 1 day for Groups 5 and 6.
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 mL dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain 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] [a] Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation.
Route:	IM
Batch Number:	To be determined
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1) Received primary vaccination at ≥ 56 years of age with either Menomune vaccine or MenACYW conjugate vaccine, as assigned by randomization, in Study MET49 or Study MET44. 2) Informed consent form has been signed and dated. 3) Able to attend all scheduled visits and to comply with all study 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 child-bearing potential and not using an effective method of contraception or abstinence for at least 4 weeks prior to vaccination and until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female

	must be post-menopausal for at least 1 year, surgically sterile, or ≥ 60 years of age. 2) Participation in the 4 weeks preceding study enrollment/vaccination or planned participation during the active phase of the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure. Note: "Active phase" refers to the period of time from revaccination with MenACYW conjugate vaccine to the end of the short-term (i.e., ~30 days) follow-up after the vaccination. Accordingly, following the blood draw at Visit 1, subjects in Group 3 and Group 4 will have a 2-year inactive phase prior to Visit 2. Prior to Visit 2, subjects in Group 3 and Group 4 will have inclusion and exclusion criteria reassessed and will continue with or be excluded from further participation in the study as appropriate. 3) Receipt of any vaccine in the 4 weeks (28 days) preceding the study vaccination or planned receipt of any vaccine during the active phase of the present study except for influenza vaccination, which may be received at least 2 weeks before or after study vaccine. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. 4) Receipt or planned receipt of any meningococcal vaccine since receipt of a single dose of MenACYW conjugate vaccine or Menomune vaccine in Study MET49 or Study MET44. 5) Receipt of immune globulins, blood, or blood-derived products in the 3 months prior to either enrollment or MenACYW conjugate vaccination in the current study. 6) 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 prior either to enrollment or MenACYW conjugate vaccination in the current study). 7) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically. 8) At high risk for meningococcal infection during the study (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). 9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the study or to a vaccine containing any of the same substances (excluding subjects in Group 5 and Group 6). 10) Verbal report of thrombocytopenia, contraindicating IM vaccination, in the Investigator's opinion (excluding subjects in Group 5 and Group 6) 11) Personal history of Guillain-Barré syndrome (GBS) (excluding subjects in Group 5 and Group 6). 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 (excluding subjects in Group 5 and Group 6). 13) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion (excluding subjects in Group 5 and Group 6), contraindicating IM vaccination in the Investigator's opinion. 14) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily. 15) Current alcohol abuse or drug addiction. 16) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion. 17) 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 or receive study vaccination until the condition has resolved or the febrile event has subsided. 18) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw. A prospective subject should not be included in the study or receive study vaccination until 72 hours have elapsed since receipt of oral or injectable antibiotic therapy. 19) 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 (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study.
Statistical Methods:	The number of subjects enrolled and their age at enrollment, sex, race, and ethnic origin will be summarized for each group, as well as the number and description of protocol deviations. In general, categorical variables will be summarized and presented by frequency counts, percentages, and 95% confidence intervals (CIs). Continuous variables will be summarized and presented with means, standard deviations, and 95% 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 geometric mean titers (GMTs), 95% CIs of point estimates will be calculated using the normal approximation assuming they are log-normally distributed. Relevant analyses will be completed for subjects in Groups 1, 2, 3, 4, 5, and 6 after completion of Stage I. After collecting all planned data for Groups 1, 2, 3, 4, 5, and 6 after completion of Stage I, the study database will be cleaned and locked. All statistical analyses planned for these groups will be conducted, and a final study report will be written. After the post-revaccination safety and immunogenicity data for Group 3 and Group 4 are collected during Stage II, the database will be updated to include the newly collected data, which will be cleaned, and the database will be relocked. Analysis of the new data will be conducted and an addendum to the clinical study report will be written.

	Primary Objective Thirty days after the administration of MenACYW conjugate vaccine, the sufficiency of the vaccine seroresponse, as assessed by the percentages of subjects who achieve an hSBA vaccine seroresponse* for meningococcal serogroups A, C, W, and Y, in Group 1 will be tested. Vaccine seroresponse will be considered sufficient if the lower limit of the 1-sided 97.5% CI for the percentage of subjects with an hSBA vaccine seroresponse against serogroups A, C, W, and Y is greater than 40%. This is equivalent to testing H0: $p \leq 0.40$ against H1: $p > 0.40$, where p is the observed proportion of subjects with hSBA vaccine seroresponse against serogroups A, C, W, and Y. The 1-sided 97.5% CI for the single proportion will be calculated using the exact method (Clopper-Pearson method). *hSBA vaccine seroresponse for serogroups A, C, W, and Y 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 Objective 1** Thirty days after the administration of MenACYW conjugate vaccine, the sufficiency of the vaccine seroresponse, as assessed by the percentages of subjects who achieve an hSBA vaccine seroresponse* for meningococcal serogroups A, C, W, and Y, in Group 2 will be tested. Vaccine seroresponse will be considered sufficient if the lower limit of the 1-sided 97.5% CI for the percentage of subjects with an hSBA vaccine seroresponse against serogroups A, C, W, and Y is greater than 40%. This is equivalent to testing H0: $p \leq 0.40$ against H1: $p > 0.40$, where p is the observed proportion of subjects with hSBA vaccine seroresponse against serogroups A, C, W, and Y. The 1-sided 97.5% CI for the single proportion will be calculated using the exact method (Clopper-Pearson method). *hSBA vaccine seroresponse for serogroups A, C, W, and Y 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 Objective 2** The proportions of subjects in a planned nonrandom subset (approximately 60 subjects from Group 1 and approximately 60 subjects from Group 2) with vaccine seroresponse for meningococcal serogroups A, C, W, and Y at 6 (window, 5–7) days following vaccination will be determined; 95% CIs of point estimates will be calculated assuming proportions follow a binomial distribution using the Exact method. No hypotheses are being tested with respect to this secondary objective. **Secondary Objective 3** For GMTs, the 95% CIs of point estimates will be calculated using the normal approximation assuming antibody titers/concentrations are log

	normally distributed. For proportions, 95% CIs of point estimates will be calculated assuming proportions follow a binomial distribution using the Exact method.
	
	Categorical variables will be summarized and presented by frequency counts, proportion 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.
	
	RCDC figures and kinetic curves will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine.
	
	Descriptive analyses on A, C, W, and Y serogroups will include:
	
	• hSBA and rSBA GMTs and corresponding 95% CIs
	• hSBA and rSBA titer distribution and RCDCs
	• Percentages of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and corresponding 95% CIs
	• Percentages of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 and corresponding 95% CIs
	Observational Objectives
	
	Immunogenicity
	For GMTs and geometric mean concentrations (GMCs), 95% CIs of point estimates will be calculated using the normal approximation assuming antibody titers/concentrations are log normally distributed. For proportions, 95% CIs of point estimates will be calculated assuming proportions follow a binomial distribution using the Exact method.
	
	Descriptive analyses on A, C, W, and Y serogroups will include:
	
	• hSBA and rSBA GMTs and corresponding 95% CIs
	• hSBA and rSBA titer distribution and RCDCs
	• Percentages of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and corresponding 95% CIs
	• Percentages of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 and corresponding 95% CIs
	• Proportion with at least a 4-fold increase in hSBA and rSBA antibody titer compared to baseline (Group 1 and Group 2 during Stage I and Group 3 and Group 4 during Stage II)
	  • An hSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as a post-vaccination titer ≥ 1:16 for subjects with pre-vaccination titer < 1:8, or a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with a pre-vaccination titer ≥ 1:8.
	  • An 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.
	• Ratio of the GMT post-vaccination/GMT pre-vaccination and the associated 95% CI of the ratio (at Day 30 for Group 1 and Group 2 and

	at Day 6 in a subset of Group 1 and Group 2 [during Stage I], and at Day 30 for Group 3 and Group 4 [during Stage II]). Descriptive analyses on anti-tetanus antibody concentrations will include: • Geometric mean concentrations at Day 0 (all groups), 2 years after enrollment (Groups 3 and 4), and 30 (window, + 14) days after the administration of a single dose of MenACYW conjugate vaccine in Study MEQ00066 (Groups 1–4) • Proportion of subjects achieving seroprotective antibody levels ≥ 0.01 IU (international units) /mL, ≥ 0.1 IU/mL, and ≥ 1.0 IU/mL to tetanus toxoid 30 (window, + 14) days after the administration of a single dose of MenACYW conjugate vaccine in Study MEQ00066 (Groups 1–4) • RCDCs and kinetic curves ***Safety*** Safety results will be described for subjects revaccinated with MenACYW conjugate vaccine (i.e., Groups 1–4). The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method). The frequency and percentage of subjects who had solicited injection site and systemic reactions and their 95% CIs will be provided. These events will be tabulated by type of reactions and intensity for each study group. These events will also be summarized by other categories specified in the endpoints (e.g., time of onset, number of days of occurrence, action taken). Unsolicited AEs will be collected, coded, and summarized by MedDRA system organ class and PT. For each unsolicited AE, the number of subjects with at least one instance of that event will be reported. Unsolicited AEs will also be tabulated by intensity and relatedness of study vaccine and by other categories specified in the endpoints. Immediate reactions, SAEs, and any event that leads to subject withdrawal from the study will be tabulated separately. **Calculation of Sample Size** **Primary Objective and Secondary Objective 1**: For Group 1 and Group 2, a sample size of 120 achieves at least 90.0% power to detect that the lower bound of the one-sided 97.5% CI is greater than 0.40 (proportion under the null hypothesis) using a 1-sided exact test with a significance level (alpha) of 0.025. For all other groups (i.e., Groups 3–6), descriptive statistics will be calculated and presented in this study; hence, no sample size or study power was calculated for these groups.

Table of Study Procedures – Groups 1 and 2: Subjects Without a Day 6 Visit

2 Visits, 1 Vaccination, 2 Blood Samples, 30 Days Duration per Subject

Visit/Contact	**Visit 1**	**Telephone Call**	**Visit 2**
Study timelines (days)	**D0**	**D08 (Visit 1 + 8 days)**	**D30 (Visit 1 + 30 days)**
Time windows (days)	**--**	+ 2 days	+ 14 days
Informed consent form	X		
Inclusion/exclusion criteria	X		
Collect subject number from Study MET49	X		
Collection of demographic data	X		
Urine pregnancy test (if applicable)	X		
Medical history	X		
Physical examination[a]	X		
Review of temporary contraindications for blood sampling[b]			X
Randomization/allocation of subject number via IRT	X		
Blood sampling (BL) 10 mL[c]	BL0001		BL0002
Vaccination[d]	X		
Immediate surveillance (30 minutes)	X		
DC provided	X		
Telephone call		X[e]	
Recording of solicited injection site and systemic reactions	D0 to D07		
Recording of unsolicited AEs, including MAAEs[f]	To be reported throughout the study period		
DC reviewed and collected			X
Reporting of SAEs, including AESIs	To be reported throughout the study period		
Collection of reportable concomitant medications	X		X
Termination of study			X

AE: adverse event; AESI: adverse event of special interest; D: day; DC: diary card; IRT; interactive response technology; MA: memory aid; MAAE: medically attended adverse event; SAE: serious adverse event

[a] Temperature needs to be measured and recorded in source documents.

[b] Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at Visit 1). 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.

[c] A pre-vaccination blood sample will be collected from all subjects at Day 0. A post-vaccination blood sample will be collected from all Group 1 and Group 2 subjects 30 (window, + 14) days following vaccination.

[d] Subjects in Groups 1 and 2 will receive 1 dose of MenACYW conjugate vaccine.

[e] This call is made 8 to10 days after the vaccinations on Day 0. If Day 8 (+2 days) 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 will remind the subject to continue using the DC up to Visit 2, to bring the DC to the study center at Visit 2, and confirm the date and time of Visit 2.

[f] MAAEs that occur between Visit 1 (Day 0) and Visit 2 will be recorded as unsolicited AEs.

Table of Study Procedures – Groups 1 and 2: Subjects With a Day 6 Visit

3 Visits, 1 Vaccination, 3 Blood Samples, 30 Days Duration per Subject

Visit Number	**Visit 1**	**Visit 2**	**Telephone Call**	**Visit 3**
Study Timelines (Days)	**D0**	**D06 (Visit 1 + 6 days)**	**D08 (Visit 1 + 8 days)**	**D30 (Visit 1 + 30 days)**
Time Windows (Days)	**--**	± 1 day	+ 2 days	+ 14 days
Informed consent	X			
Inclusion/exclusion criteria	X			
Collect subject number from Study MET49	X			
Collection of demographic data	X			
Urine pregnancy test (if applicable)	X			
Medical history	X			
Physical examination[a]	X			
Review of temporary contraindications for blood sampling[b]		X		X
Randomization/allocation of subject number via IRT	X			
Blood sampling (BL) – 10 mL[c]	BL0001	BL0002[d]		BL0003
Vaccination[e]	X			
Immediate surveillance (30 minutes)	X			
DC provided	X			
Telephone call[f]			X	
Recording of solicited injection site and systemic reactions	D0 to D07			
Recording of unsolicited AEs, including MAAEs[g]	To be reported throughout the study period			
DC reviewed and collected				X
Reporting of SAEs, including AESIs	To be reported throughout the study period			
Collection of reportable concomitant medications	X	X		X
Termination of study				X

AE: adverse event; AESI: adverse event of special interest; D: day; DC: diary card; IRT: interactive response technology; MAAE: medically attended adverse event; SAE: serious adverse event

[a] Temperature needs to be measured and recorded in source documents.

[b] Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second or third 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 (6 [window, 5–7] days after vaccination at Visit 1 and 30 [window, + 14] days after vaccination at Visit 1). 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.

[c] A pre-vaccination blood sample will be collected from all subjects at Day 0. A post-vaccination blood sample will be collected from all subjects in the Group 1 and Group 2 subset approximately 6 (window, 5–7) days and 30 (window, + 14) days following vaccination.

[d] A planned total of 120 subjects (the first 60 subjects in Group 1 and the first 60 subjects in Group 2).

[e] Subjects in Groups 1 and 2 will receive 1 dose of MenACYW conjugate vaccine.

[f] This call is made 8 to 10 days after the vaccinations on Day 0. If Day 8 (+2 days) 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 will remind the subject to continue using the DC up to Visit 3, to bring the DC to the study center at Visit 3, and confirm the date and time of Visit 3.

[g] MAAEs that occur between Visit 1 (Day 0) and Visit 3 will be recorded as unsolicited AEs.

Table of Study Procedures – Groups 3 and 4

3 Visits, 1 Vaccination, 3 Blood Samples, 2 years + 30 Days Duration Per Subject

Visit/Contact	**Visit 1**	**Telephone Call**		**Visit 2**	**Telephone Call**	**Visit 3**
Study timelines (days)	**D0**	**Visit 1 + 8 days**		**Visit 1 + 2 years**	**Visit 2 + 8 days**	**Visit 2 + 30 days**
Time windows (days)	--	+ 2 days		+ 44 days	+ 2 days	+ 14 days
Informed consent form	X					
Inclusion/exclusion criteria	X			X		
Collect subject number from Study MET49	X					
Collection of demographic data	X					
Urine pregnancy test (if applicable)	X			X		
Medical history	X			X		
Physical examination[a]	X			X		
Review of temporary contraindications for blood sampling[b]				X		X
Randomization/allocation of subject number via IRT	X					
Blood sampling (BL) 10 mL[c]	BL0001			BL0002		BL0003
Immediate surveillance after blood sampling (15 minutes) for the occurrence of a syncopal episode	X					
MA provided to collect any SAEs related to blood sampling performed at Visit 1	X					
Vaccination[d]				X		
Immediate surveillance (30 minutes)				X		
DC provided				X		
Telephone call		X[e]			X[f]	
Recording of solicited injection site and systemic reactions				Visit 2 + 7 days		
Recording of unsolicited AEs, including MAAEs[g]				Visit 2 through Visit 3		

Visit/Contact	**Visit 1**	**Telephone Call**		**Visit 2**	**Telephone Call**	**Visit 3**
Study timelines (days)	**D0**	**Visit 1 + 8 days**		**Visit 1 + 2 years**	**Visit 2 + 8 days**	**Visit 2 + 30 days**
Time windows (days)	--	+ 2 days		+ 44 days	+ 2 days	+ 14 days
DC reviewed and collected						X
Periodic follow-up during inactive phase of study (i.e., at least 1 call every 3 months)			X			
Reporting of SAEs, including AESIs	X			To be reported throughout the study period		
Collection of reportable concomitant medications	X			X		X
Termination of study						X

AE: adverse event; AESI: adverse event of special interest; D: day; DC: diary card; IRT: interactive response technology; MA: memory aid; MAAE: medically attended adverse event; SAE: serious adverse event

[a] Temperature needs to be measured and recorded in source documents.

[b] Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second or third blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 [window, + 14] days after vaccination at Visit 2). 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.

[c] A blood sample will be collected from all subjects at Visit 1, at Visit 2 prior to vaccination, and at Visit 3 approximately 30 (window, + 14) days after vaccination.

[d] Subjects will receive 1 dose of MenACYW conjugate vaccine.

[e] This call is made 8 to10 days after blood sampling at Visit 1. If Visit 1 + 8 (window, +2) days 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 SAEs in the first 3 days after blood sampling.

[f] This call is made 8 to10 days after the vaccinations at Visit 2. If Visit 2 + 8 (window, +2) days 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 will remind the subject to continue using the DC up to Visit 3, to bring the DC to the study center at Visit 3, and confirm the date and time of Visit 3.

[g] MAAEs will be recorded as unsolicited AEs.

Table of Study Procedures – Groups 5 and 6

1 Visit, 1 Blood Sample, 1 Day Duration per Subject

Visit/Contact	**Visit 1**	**Telephone Call**
Study timelines (days)	**D0**	**D08 (Visit 1 + 8 days)**
Time windows (days)	--	+ 2 days
Informed consent form	X	
Inclusion/exclusion criteria	X	
Collect subject number from Study MET44	X	
Collection of demographic data	X	
Medical history	X	
Physical examination[a]	X	
Allocation of subject number via IRT	X	
Blood sampling (BL) 10 mL	BL0001	
Immediate surveillance after blood sampling (15 minutes) for the occurrence of a syncopal episode	X	
MA provided to collect any SAEs related to blood sampling performed at Visit 1	X	
Telephone call[b]		X
Reporting of SAEs related to study procedures	X	
Collection of reportable concomitant medications	X	
Termination of study	X	

IRT: interactive response technology; SAE: serious adverse event

[a] Temperature needs to be measured and recorded in source documents.

[b] This call is made 8 to10 days after blood sampling at Visit 1. If Visit 1 + 8 (window, +2) days 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 SAEs in the first 3 days after blood sampling.

List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
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
CSR	Clinical Study Report
ECL	Electrochemiluminescence
EDC	Electronic Data Capture
FAS	Full Analysis Set
FVFS	First Visit, First Subject
GBS	Guillain-Barré Syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GPV	Global Pharmacovigilance
hSBA	Serum Bactericidal Assay Using Human Complement
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular
IMD	Invasive Meningococcal Disease
IME	Important Medical Event
IOM	Institute of Medicine
IRB	Institutional Review Board
IRT	Interactive Response Technology
LLOQ	Lower Limit of Quantification
LLT	Lowest Level Term
LVLS	Last Visit, Last Subject
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities

MTL	Medical Team Leader
PPAS	Per-Protocol Analysis Set
rSBA	Serum Bactericidal Assay Using Baby Rabbit Complement
RMO	Responsible Medical Officer
SAE	Serious Adverse Event
TMF	Trial Master File
ULOQ	Upper Limit of Quantification
US	United States

1 Introduction

1.1 Background

This is a study using MenACYW conjugate vaccine against invasive meningococcal disease (IMD).

Meningococcal disease is caused by the gram-negative aerobic diplococcus *Neisseria meningitidis*, an exclusively human pathogen. Meningococci colonize the nasopharynx of an estimated 10% to 20% of the population at any given time and are transmitted by respiratory secretions (1).Yet, only a small proportion of carriers develop invasive disease, and predicting an individual's risk is difficult.

The 2 most common clinical presentations are meningococcemia or sepsis, which is accompanied by a petechial or purpuric rash in the majority of patients, and purulent meningitis. Despite appropriate treatment, the overall mortality rate for meningococcal disease has been reported to be 7%–19% (2). Approximately 10%–20% of cases result in permanent disabilities such as limb loss, deafness, seizures, or psychomotor retardation.

The current classification system for identifying meningococci by serogroup is based on the immunochemistry of the polysaccharide capsule surrounding the bacterium (3). The capsule is a major virulence factor of *N. meningitidis*. At least 12 distinct meningococcal serogroups have been classified based on the biochemical structure of the capsular polysaccharides (4). Of these, *N. meningitidis* serogroups A, B, C, W, X, and Y are responsible for most cases of disease (5).

N. meningitidis causes both endemic and epidemic disease. Over 500,000 cases of meningococcal disease occur worldwide per year, resulting in approximately 135,000 deaths (6). The incidence of meningococcal disease has been steadily decreasing in the United States since the late 1990s. During 2012–2015, there were 350–550 cases reported annually with an incidence of 0.1–0.2 cases per 100,000 population (7). The peak incidence of disease occurs during the winter and early spring. With respect to age, the highest rates of meningococcal disease in the United States occur among infants and children aged < 5 years, followed by a second peak among adolescents and young adults aged 16 through 21 years, and a third peak in adults aged ≥ 65 years. In the latter age group, the highest case-fatality ratio (23.8%) is observed (8).

The epidemiology of meningococcal disease varies by the causative serogroup. Serogroups A, B, C, and W-135 have caused large epidemics worldwide. Serogroup A remains the leading cause of meningococcal disease in developing countries, particularly in the so-called meningitis belt of sub-Saharan Africa where it can cause tens of thousands of cases annually. More recently, serogroup W-135 disease has been associated with Hajj pilgrims and epidemics in sub-Saharan Africa. Serogroups B and C predominate in developed countries. In the United States, disease is most commonly due to serogroups B, C, and Y, with serogroup Y disease having emerged as a more common threat within the past 2 to 3 decades and accounting for about one-third of reported cases in recent years (9) (10). Approximately 60% of cases among adults aged ≥ 65 years are caused by serogroup Y, and 43% are characterized by bacteremic pneumonia (8).

To help prevent IMD among those considered at increased risk for the disease, vaccination is recommended (11). For example, the Advisory Committee on Immunization Practices

recommends that travelers who visit or reside in the so-called meningitis belt during the dry season (December–June) receive vaccination with a quadrivalent (serogroup A, C, W, and Y) meningococcal vaccine before travel. In addition, Kingdom of Saudi Arabia visitors travelling to the Hajj and Umrah are required to submit a valid vaccination certificate indicating administration of either a quadrivalent polysaccharide meningococcal vaccine within the last 3 years or a quadrivalent conjugate vaccine within the last 5 years (12). This requirement stems from evidence demonstrating that protection following MenACWY vaccination may wane 3 to 5 years after primary vaccination (8) (13) (14) (15).

1.2 Background of the Investigational Product

MenACYW conjugate vaccine is designed for active immunization of individuals 6 weeks of age and older, including older adults ≥ 56 years of age, against IMD. The purpose of the vaccine is to provide broad coverage against circulating meningococcal strains from serogroups A, C, W, and Y. In contrast to the previous Sanofi Pasteur meningococcal conjugate vaccine, MenACYW conjugate vaccine is prepared by using tetanus toxoid as the carrier protein. Conjugation of polysaccharide antigens to a protein carrier can induce T-cell-dependent immune responses, which have been shown to give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response. The program targets licensure of MenACYW conjugate vaccine in many countries in North America, Europe, Latin America, Africa, the Middle East, and Asia Pacific.

Meningococcal polysaccharide vaccines have 2 important limitations: a) the antibody response is age-dependent, with the poorest response seen in infants; and b) polysaccharides alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of polysaccharide vaccines in infants and children has been shown to be improved by conjugating the polysaccharides to protein carriers. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies, using a mouse model and investigating different carriers, showed significant levels of polysaccharide-specific total immunoglobulin G (IgG) and bactericidal antibodies in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials, including those evaluating the final formulation of MenACYW conjugate vaccine (studies MET39 and MET44), showed the potential of the candidate vaccine to be a potent immunogen in all age groups, including young infants and older adults.

All of the core components of MenACYW conjugate vaccine have been used extensively in licensed vaccines and have been shown to be safe. The meningococcal polysaccharides are the same as those used in Menactra® and Menomune® - A/C/Y/W-135 vaccines, and the source of tetanus toxoid protein used as a protein carrier in MenACYW conjugate vaccine is the same as that used in ActHIB® (a vaccine against *Haemophilus influenzae* type b [Hib]), in the Hib portion of Pentacel® (DTaP5-IPV//Hib), and as the tetanus antigen in Hexaxim® (DTaP2-IPV-Hep B-Hib). The safety of the combination of these components as they are used in MenACYW conjugate vaccine has been evaluated in 6 Phase I/II clinical trials and in 10 Phase III clinical trials as part of the development program in adults, toddlers, and infants. Two of these studies (MET44 and MET49) were conducted in subjects ≥ 56 years of age and evaluated the safety and

immunogenicity of MenACYW conjugate vaccine compared to quadrivalent plain polysaccharide meningococcal (Menomune) vaccine:

- MET44 (Phase II, 2012) enrolled 301 subjects who were randomly assigned to receive either MenACYW conjugate or Menomune vaccine. Within each vaccine group, subjects were stratified into 2 age groups, 56 to 64 years and ≥ 65 years of age. Proportions of subjects demonstrating antibody titers ≥ 1:8 with serum bactericidal assay using human complement (hSBA) following administration of MenACYW conjugate vaccine were similar to, or for serogroups W and Y, higher than those for subjects who received Menomune vaccine. Within each group of subjects who received MenACYW conjugate or Menomune vaccine, proportions of subjects with hSBA titers ≥ 1:8 were comparable between the 56 to 64 year and ≥ 65 year age subgroups.
- MET49 (Phase III, 2016–2017) enrolled 907 subjects who were randomly assigned to receive either MenACYW conjugate or Menomune vaccine. Within each vaccine group, subjects were stratified into 2 age groups, 56 to 64 years and ≥ 65 years of age. Thirty days after vaccination, the seroresponse of MenACYW conjugate vaccine was demonstrated to be non-inferior to that of Menomune vaccine for all 4 serogroups as measured by hSBA. Seroresponse was defined by either a post-vaccination titer of ≥ 1:16 for subjects with a pre-vaccination titer < 1:8, or at least a 4-fold rise in titer for subjects with a pre-vaccination titer ≥ 1:8. Geometric mean titers (GMTs) were higher for the MenACYW conjugate vaccine group than for the Menomune vaccine group for all serogroups. For subjects 56 to 64 years of age and subjects ≥ 65 years of age, immunogenicity was comparable to immune responses in the overall study population of adults ≥ 56 years of age.

Overall, vaccination with MenACYW conjugate vaccine was found to be well tolerated, with no safety concerns identified. Solicited reactions, both injection site and systemic reactions, were more frequently reported in subjects aged 56 to 64 years than in subjects aged ≥ 65 years for both the MenACYW conjugate vaccine and Menomune vaccine groups. The rates of solicited reactions, particularly injection site reactions, were higher in subjects who received MenACYW conjugate vaccine than in subjects who received Menomune vaccine; however, no increase in the severity of these reactions was observed. The observed differences in local reactogenicity are likely attributable to differences in formulation (use of tetanus toxoid as a protein carrier in MenACYW vaccine vs. no use of a protein carrier in Menomune vaccine) and differences in routes of administration (intramuscular [IM] for MenACYW conjugate vaccine vs. subcutaneous for Menomune vaccine).

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 may be no direct benefit from receiving the MenACYW conjugate vaccine. However, based on the data generated from previous studies, the immunogenicity profile of the MenACYW conjugate vaccine in different age groups shows that the majority of subjects developed seroprotective levels of antibodies after vaccination. The safety evaluation indicates

that the vaccine is well-tolerated, with no safety concerns having been detected to date. In all, the data support further evaluation of the MenACYW conjugate vaccine in humans.

Subjects who receive MenACYW conjugate vaccine will likely be protected against meningococcal disease caused by *N. meningitidis* serogroups A, C, W, and Y. As with any vaccine, MenACYW conjugate vaccine may not protect 100% of individuals against the diseases the vaccine is designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine may cause local reactions such as pain, swelling, erythema, pruritus, warmth, and ecchymosis at the injection site, or certain systemic events such as fever, headache, malaise, or myalgia. There may be a rare possibility of an allergic reaction, which could be severe. There may be other risks for MenACYW conjugate vaccine that are not yet known.

The following additional adverse events (AEs) have been reported during post-approval use of the United States (US)-licensed quadrivalent meningococcal conjugate vaccine manufactured by the Sponsor, Menactra vaccine, which contains detoxified diphtheria toxoid as a protein carrier: Guillain-Barré syndrome (GBS), transverse myelitis, acute disseminated encephalomyelitis, vasovagal syncope, facial palsy, dizziness, paraesthesia, convulsion, and hypersensitivity reactions such as anaphylactic/anaphylactoid reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, and hypotension. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to Menactra vaccine exposure.

Guillain-Barré syndrome has been reported mostly in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of a US licensed quadrivalent meningococcal conjugate vaccine, Menactra vaccine (16). A retrospective cohort study carried out in the United States using healthcare claims data found no evidence of increased GBS risk associated with the use of that vaccine. This study was able to exclude all but relatively small incremental risks (17).

Because the MenACYW conjugate vaccine used in this study contains tetanus toxoid as a protein carrier, experience with tetanus toxoid antigen is relevant. 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 (18). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (17). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (18).

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 serious adverse event (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 workup 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. No other SAEs reported in completed or ongoing clinical trials were considered by the Investigator as related to MenACYW conjugate vaccine.

The risk of vasovagal syncope exists after any vaccination, although it has not been specifically reported after MenACYW conjugate vaccine in the age group under study as part of this protocol.

The potential risks listed here are not exhaustive. Refer to the Investigational Brochure for MenACYW conjugate vaccine for additional information regarding the potential risks.

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

1.4 Rationale for the Study

The purpose of MEQ00066 is to further evaluate MenACYW conjugate vaccine in older adults, including those ≥ 65 years of age, which is the age group that has the third highest incidence of meningococcal disease in the United States (0.5 cases per 100,000 population) and the highest case-fatality ratio (23.8%) (8). Specifically, MEQ00066 seeks to assess the safety and immunogenicity of a single dose of MenACYW conjugate vaccine ≥ 3 years after a primary vaccination with Menomune vaccine or MenACYW conjugate vaccine in subjects who were ≥ 56 years of age at primary vaccination. Data from this study are intended to support use of MenACYW conjugate vaccine in older adults who previously received a polysaccharide vaccine and might be in need of repeat meningococcal vaccination because of increased risk of exposure (e.g., travel to an area where meningococcal disease is hyperendemic or epidemic). Antibody persistence 3, 5, or 7 years following a primary dose of either Menomune vaccine or MenACYW conjugate vaccine will also be evaluated. [redacted] titers will be determined using both hSBA and serum bactericidal assay using baby rabbit complement (rSBA).

No early safety data review is planned for this study as MenACYW conjugate vaccine has been previously administered to more than 5000 infants, toddlers, children, adolescents, and adults, including over 650 older adults (i.e., ≥ 56 years of age) with no confirmed safety signals occurring in the clinical trials completed to date. MenACYW conjugate vaccine has been well tolerated regardless of the immunization schedule and the number of doses administered (e.g., up to 4 doses in young children, with the minimal interval between each dose being approximately 2 months).

[redacted]

2 Study Objectives

2.1 Primary Objective

To demonstrate sufficiency of the vaccine seroresponse to meningococcal serogroups A, C, W, and Y following administration of a single dose of MenACYW conjugate vaccine to Group 1 subjects (who received primary vaccination with Menomune vaccine ≥ 3 years earlier at ≥ 56 years of age in Study MET49).

The endpoint for the primary objective is presented in Section 9.1.1.1.

2.2 Secondary Objectives

Secondary Objective 1

- To demonstrate sufficiency of the vaccine seroresponse to meningococcal serogroups A, C, W, and Y following administration of a single dose of MenACYW conjugate vaccine to Group 2 subjects (who received primary vaccination with MenACYW conjugate vaccine ≥ 3 years earlier at ≥ 56 years of age in Study MET49).

Secondary Objective 2

- To describe vaccine seroresponse rates with respect to serogroups A, C, W, and Y in serum specimens collected 6 (window, 5–7) days post-vaccination in approximately 60 subjects from Group 1 (Menomune-primed) and approximately 60 subjects from Group 2 (MenACYW conjugate vaccine-primed).

Secondary Objective 3

- To describe antibody persistence ≥ 3 years after primary vaccination with Menomune vaccine or MenACYW conjugate vaccine for subjects from all groups.

The endpoints for the secondary objective are presented in Section 9.2.1.1.

2.3 Observational Objectives

Immunogenicity

- To describe the immunogenicity of a single dose of MenACYW conjugate vaccine, as assessed by hSBA and rSBA antibody titers, among persons who previously received Menomune vaccine or MenACYW conjugate vaccine ≥ 3 years earlier.
- To describe antibody levels against tetanus toxoid at enrollment (all groups), 2 years after enrollment (Groups 3 and 4), and 30 (window, + 14) days after a single dose of MenACYW conjugate vaccine (Groups 1–4) in Study MEQ00066.

Safety

To describe the safety profile of a single dose of MenACYW conjugate vaccine administered to adults who received Menomune vaccine or MenACYW conjugate vaccine ≥ 3 years earlier (Groups 1 and 2 during Stage I; Groups 3 and 4 during Stage II).

The endpoints for the immunogenicity and safety observational objectives are presented in Section 9.3.1.1 and Section 9.3.2.2, respectively.

3 Investigators and Study Organization

This study will be conducted in 34 centers in in the United States. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator. Details of the study centers, the Investigators at each center, and the Coordinating Investigator are provided in the "List of Investigators and Centers Involved in the Trial" document.

The Sponsor's Responsible Medical Officers (RMOs) (the persons authorized to sign this protocol and any amendments on behalf of the Sponsor) are [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), 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 Institutional Review Board(s) (IRB[s]).

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 IRB(s) (the names and qualifications of the members attending and voting at the meetings).

The Investigator and Sponsor will submit written summaries of the status of the study to the IRB annually, or more frequently if requested. All SAEs occurring during the study that are related to the product administered will be reported by the Investigator to the IRB, according to the IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This will be a Phase III, 2-stage, randomized, open-label, multi-center study to evaluate the safety and immunogenicity of a single dose of MenACYW conjugate vaccine ≥ 3 years after a prior dose of either Menomune vaccine or MenACYW conjugate vaccine in subjects ≥ 56 years of age at the time of primary vaccination. Antibody persistence after primary vaccination with Menomune vaccine or MenACYW conjugate vaccine will also be evaluated. The study will be conducted in 2 stages.

Subjects who received Menomune vaccine or MenACYW conjugate vaccine in Study MET49 or Study MET44 are eligible for enrollment in Study MEQ00066.

A planned minimum of 440 subjects who participated in Study MET49 (i.e., 3 years prior to enrollment in the current study) will be randomly assigned to Group 1 or Group 3, or Group 2 or Group 4, depending on the vaccine originally received in Study MET49. These subjects will have antibody persistence assessed, followed by receipt of a single dose of MenACYW conjugate vaccine as per the stages described below.

Stage I:

Group 1: Approximately 180 subjects who received Menomune vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 (to assess antibody persistence 3 years after primary vaccination), followed by receipt of a single dose of MenACYW conjugate vaccine (ratio 9:2 [Group 1:Group 3]). The first 60 subjects enrolled in Group 1 will comprise a subset from which an additional blood sample will be obtained at 6 (window, 5–7) days post-vaccination.

Group 2: Approximately180 subjects who received MenACYW conjugate vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 (to assess antibody persistence 3 years after primary vaccination), followed by receipt of a single dose of MenACYW conjugate vaccine (ratio 9:2 [Group 2:Group 4]). The first 60 subjects enrolled in Group 2 will comprise a subset from which an additional blood sample will be obtained at 6 (window, 5–7) days post-vaccination.

Group 3: Approximately 40 subjects who received Menomune vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 for the assessment of antibody persistence 3 years after primary vaccination.

Group 4: Approximately 40 subjects who received MenACYW conjugate vaccine in Study MET49 will provide a blood sample at enrollment in Study MEQ00066 for the assessment of antibody persistence 3 years after primary vaccination.

A planned total of 120 subjects who participated in Study MET44 (i.e., 6–7 years prior to enrollment in the current study) will provide a blood sample at enrollment in Study MEQ00066

for the assessment of antibody persistence 6–7 years after primary vaccination with either Menomune vaccine or MenACYW conjugate vaccine. These subjects will not receive a vaccination with MenACYW conjugate vaccine at enrollment. The subjects will be grouped as follows:

Group 5: 60 subjects who received Menomune vaccine in Study MET44

Group 6: 60 subjects who received MenACYW conjugate vaccine in Study MET44

Stage II (2 years after enrollment)

Group 3: The approximately 40 subjects who were randomly assigned to this group at the time of initial enrollment in Study MEQ00066 will provide an additional blood sample (to assess antibody persistence at 5 years), followed by receipt of a single dose of MenACYW conjugate vaccine.

Group 4: The approximately 40 subjects who were randomly assigned to this group at the time of initial enrollment in Study MEQ00066 will provide an additional blood sample (to assess antibody persistence at 5 years), followed by receipt of a single dose of MenACYW conjugate vaccine.

The study design is summarized in Table 5.1.

Table 5.1: MEQ00066 Study Design

Stage	Group	Vaccine Received in MET49	Vaccine Received in MET44	Antibody Persistence	Will Receive MenACYW Conjugate Vaccine in MEQ00066	Planned Sample Size
I	**1**	Menomune		3 years	Yes	180
	2	MenACYW		3 years	Yes	180
	3	Menomune		3 years	At Stage II	40
	4	MenACYW		3 years	At Stage II	40
	5		Menomune	7 years	No	60
	6		MenACYW	7 years	No	60
II	**3**	Menomune		5 years	Yes	See Stage I
	4	MenACYW		5 years	Yes	See Stage I

5.1.2 Justification of the Study Design

This study is part of the ongoing clinical development program that focuses on demonstrating the safety and immunogenicity of MenACYW conjugate vaccine. MEQ00066 is a study that will be

conducted as part of the Phase III of development of the MenACYW conjugate vaccine in which the vaccine would be evaluated in older adults who previously received a meningococcal vaccine at 56 years of age or older during Study MET49 or Study MET44. Since MenACYW conjugate vaccine has been evaluated in infants, toddlers, and adults (including adults 56 years of age and older) without raising any safety concerns, safety assessments will be done up to 30 days after vaccination.

The study is open label, as only 1 vaccine will be administered.

See Section 1.4 for the justification for the selection of subjects and the choice of groups.

5.1.3 Study Plan

Vaccination

- Subjects in Groups 1 and 2 will receive a single dose of MenACYW conjugate vaccine at Visit 1.
- Subjects in Groups 3 and 4 will receive a single dose of MenACYW conjugate vaccine 2 years after the enrollment visit (i.e., approximately 5 years after having received primary vaccination in Study MET49).
- Subjects in Groups 5 and 6 will not receive a vaccination.

Blood Sampling

- All subjects (Groups 1–6) will provide a blood sample at enrollment (Visit 1) to be tested for antibody persistence 3 years (Groups 1–4) or 6–7 years (Groups 5 and 6) after having received primary vaccination in Study MET49 or Study MET44, respectively.
- Subjects in Groups 1 and 2 will provide a blood sample 30 (window, + 14) days after receiving a single dose of MenACYW conjugate vaccine at Visit 1. A subset of subjects, approximately 60 in Group 1 and 60 in Group 2, will also provide a blood sample 6 (window, 5–7) days following vaccination.
- Subjects in Groups 3 and 4 will provide 2 additional blood samples after enrollment: 1 at 2 years (window, + 44 days) after the enrollment visit prior to vaccination with a single dose of MenACYW conjugate vaccine and 1 at 30 (window, + 14) days post-vaccination.

Handling of Low Serum Bactericidal Antibody Levels (Groups 5 and 6 Only)

- It is possible that some subjects in Groups 5 and 6 may have hSBA titers < 1:8 (the putative level of protection against IMD) to 1 or more of vaccine serogroups (A, C, W, or Y). Investigators will be informed of and notify all subjects in Groups 5 and 6 whose hSBA titers are < 1:8.

Handling of Low Serum Antitetanus Antibody Levels (All Groups)

- Regardless of group assignment, it is possible that some subjects may have serum antitetanus antibody titers < 0.1 IU/mL (the putative level of protection against tetanus disease). Investigators will be informed of and notify all subjects whose antitetanus antibody titers are < 0.1 IU/mL.

Collection of Safety Data

Collection of safety data for subjects who are revaccinated with MenACYW conjugate vaccine (i.e., subjects in Groups 1 and 2 during Stage I, and subjects in Groups 3 and 4 during Stage II)

Staff will observe subjects for 30 minutes following vaccination and will record the occurrence of any immediate unsolicited systemic AEs. Subjects will record information about solicited injection site and systemic reactions from Day 0 through Day 7 after vaccination. Information on unsolicited AEs, including medically attended adverse events (MAAEs), adverse events of special interest (AESIs), and SAEs, will be collected from Day 0 through ~Day 30 after vaccination.

Collection of safety data for subjects in Groups 3 and 4 after Visit 1 and Groups 5 and 6 during Stage I

Safety follow-up for subjects in Groups 3 and 4 after Visit 1 and Group 5 and Group 6 will be limited to the collection of SAEs considered by the Investigator to be related to study procedures (e.g., blood sampling).

Pregnancy Testing

A urine human chorionic gonadotropin pregnancy test supplied by Sanofi Pasteur will be used to test females of child-bearing potential for pregnancy prior to vaccination. Subjects will not participate in the study if the initial pregnancy test was positive. For the purposes of the study, female subjects ≥ 60 years of age are defined as not of childbearing potential.

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 licenses/credentials.

5.1.4.1 Groups 1 and 2

Visit 1 (Day 0): Inclusion, Randomization, Blood Sample, and Vaccination

1) Explain the study objectives and design to the subject, including but not limited to its objectives, design, and risks and benefits, and answer any questions the subject may have.
2) Obtain a signed informed consent from the subject. The Investigator or delegate will also sign and date the ICF, retain the original, and give a copy of the signed and dated form to the subject.
3) Check eligibility of the subject by reviewing applicable inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively).
4) Collect subject number from Study MET49.
5) Collect relevant demographic data.
6) When applicable, perform a urine pregnancy test.
7) Obtain significant medical history (see Section 5.2.6 for details)
8) Perform a directed physical examination, if indicated, based on medical history.

9) Measure the temperature by the preferred route (see Section 9.3.2.3.2) and record this information in the source document. If the temperature is ≥ 100.4°F (38.0°C), defer enrollment until the subject is afebrile for at least 24 hours.
10) If the subject meets all inclusion and no exclusion criteria, connect to the interactive response technology (IRT) system for randomization, group assignment, and allocation of subject number (see Section 6.5 for instructions).
11) Obtain a pre-vaccination blood sample (approximately 10 mL; see Section 7.1 for details regarding the collection 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 inclusion/exclusion criteria must be re-validated.
12) Prepare vaccine to be administered based on the information provided in Section 6.1.1.2.
13) Within 30 minutes of removing the MenACYW vaccine from the refrigerator, inject 1 dose of vaccine into the deltoid muscle of the arm (see Section 6.1.1.2).
14) Observe the subject for 30 minutes following the injection and record any AE in the source document.
15) Provide the subject a diary card, a digital thermometer, and a flexible ruler, along with instructions for their use, to record solicited injection site and systemic reactions from Day 0 through Day 7 post-vaccination, unsolicited AEs and SAEs, as well as any concomitant medications (see Section 6.7) from Visit 1 to 30 (window, + 14) days post-vaccination.
16) Schedule the next visit.
17) Remind the subject that they will be contacted by telephone on or about Day 8 post-vaccination to remind them to complete the diary card and to bring the completed diary card with them to Visit 2 or Visit 3 (for subjects in the Day 6 subset).
18) Remind the subject to notify the site immediately if an SAE occurs.
19) Collect reportable concomitant medications (see Section 6.7).
20) Complete the relevant case report forms (CRFs) for this visit.

Visit 2 (Day 6): Blood Sample - Subjects in the Day 6 Subset Only

1) Review the temporary contraindications for blood sampling (see Section 5.2.8).
2) Obtain the second blood sample (approximately 10 mL; see Section 7.1 for details regarding the collection of blood samples).
3) Collect reportable concomitant medications (see Section 6.7).
4) Complete the relevant CRFs for this visit.

Telephone Contact – Visit 1 + 8 (window, 8–10) Days

Note: If Day 8 falls on a weekend or a holiday, the telephone call may be made on the following business day. If the subject is not available, the study staff should document the attempts to make contact.

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 to do the following:
   - Complete the remaining pages of the diary card and bring them to Visit 2 or Visit 3 (for subjects in the Day 6 subset).
   - Notify the site immediately if an SAE occurs.

Final Visit (Visit 2 or Visit 3 [for subjects in the Day 6 subset]) (30 [+ 14] days after Visit 1): Collection of Safety Information and Blood Sample

1) Collect the diary card and review each page with the subject, including any AEs, medications, or therapy that occurred since vaccination.
2) Review the temporary contraindications for blood sampling (see Section 5.2.8).
3) Obtain the blood sample (approximately 10 mL; see Section 7.1 for details regarding the collection of blood samples).
4) Collect reportable concomitant medications (see Section 6.7).
5) Complete the relevant CRFs for this visit and the End of Study CRF.
6) If the subject does not return for Visit 2 (Visit 3 for subjects in the Day 6 subset), and the diary card is not received at the site, site personnel will contact the subject by telephone. During the telephone call, the subject 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 with 3 attempts, the study personnel will follow instructions given in Section 5.2.10.

5.1.4.2 Groups 3 and 4

Visit 1 (Day 0): Inclusion, Randomization, and Blood Sample

1) Explain the study objectives and design to the subject, including but not limited to its objectives, design, and risks and benefits, and answer any questions the subject may have.
2) Obtain a signed informed consent from the subject. The Investigator or delegate will also sign and date the ICF, retain the original, and give a copy of the signed and dated form to the subject.
3) Check eligibility of the subject by reviewing applicable inclusion and exclusion criteria eligibility (see Section 5.2.4 and Section 5.2.5, respectively).
4) Collect subject number from Study MET49.
5) Collect relevant demographic data.

6) When applicable, perform a urine pregnancy test.
7) Obtain significant medical history (see Section 5.2.6 for details).
8) Perform a directed physical examination, if indicated, based on medical history.
9) Measure the temperature by the preferred route (see Section 9.3.2.3.2) and record this information in the source document. If the temperature is ≥ 100.4°F (38.0°C), defer enrollment until the subject is afebrile for at least 24 hours.
10) If the subject meets all inclusion and no exclusion criteria, connect to the IRT system for randomization, group assignment, and allocation of subject number (see Section 6.5 for instructions).
11) Obtain the first blood sample (approximately 10 mL; see Section 7.1 for details regarding the collection 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 inclusion/exclusion criteria must be re-validated.
12) Observe the subject for 15 minutes following blood sampling for the occurrence of a syncopal episode.
13) Collect any SAEs related to study procedures.
14) Provide the subject with a memory aid to record any SAEs related to blood sampling for the first 3 days after Visit 1.
15) Remind the subject that they will be contacted by telephone on or about Day 8 post-Visit 1 to ask them about any SAEs that might be related to blood sampling.
16) Remind the subject to notify the site immediately if an SAE occurs.
17) Collect reportable concomitant medications (see Section 6.7).
18) Schedule the next visit.
19) Complete the relevant CRFs for this visit.

Periodic Telephone Contact During the 2-Year Inactive Phase

1) Subjects will receive periodic follow-up calls (e.g., at least 1 call every 3 months) during the 2-year inactive phase.
2) Record relevant information concerning the subject's health status on the telephone contact form.

Visit 2 (2 years after Visit 1): Blood Sample, Vaccination, and Collection of Safety Information

1) Check eligibility of the subject by reviewing applicable inclusion and exclusion criteria eligibility (see Section 5.2.4 and Section 5.2.5, respectively).
2) When applicable, perform a urine pregnancy test.
3) Obtain significant medical history (see Section 5.2.6 for details).
4) Perform a directed physical examination, if indicated, based on medical history.

5) Measure the temperature by the preferred route (see Section 9.3.2.3.2) and record this information in the source document. If the temperature is ≥ 100.4°F (38.0°C), defer Visit 2 until the subject is afebrile for at least 24 hours.
6) Review the temporary contraindications for blood sampling (see Section 5.2.8).
7) Obtain the second blood sample (approximately 10 mL; see Section 7.1 for details regarding the collection of blood samples). If attempts to obtain the second blood draw are unsuccessful (3 attempts), then Visit 2 can be rescheduled to a later date at which point inclusion/exclusion criteria must be re-validated.
8) Prepare vaccine to be administered based on the information provided in Section 6.1.1.2.
9) Within 30 minutes of removing the MenACYW vaccine from the refrigerator, inject 1 dose of the vaccine into the deltoid muscle of the arm (see Section 6.1.1.2).
10) Observe the subject for 30 minutes following the injection and record any AE in the source document.
11) Provide the subject with a diary card, a digital thermometer, and a flexible ruler, along with instructions for their use, to record solicited injection site and systemic reactions from Day 0 through Day 7 post-vaccination, unsolicited AEs and SAEs, as well as any concomitant medications (see Section 6.7) from Visit 2 to 30 (window, + 14) days post-vaccination.
12) Schedule Visit 3.
13) Remind the subject that they will be contacted by telephone on or about Day 8 post-vaccination to remind them to complete the diary card and to bring the diary card with them to Visit 3.
14) Remind the subject to notify the site immediately if an SAE occurs.
15) Collect reportable concomitant medications (see Section 6.7).
16) Complete the relevant CRFs for this visit.

Telephone Contact – Visit 2 + 8 (window, 8–10) Days

Note: If Day 8 falls on a weekend or a holiday, the telephone call may be made on the following business day. If the subject is not available, the study staff should document the attempts to make contact.

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 to do the following:
   - Complete the remaining pages of the diary card and bring them to Visit 3.
   - Notify the site immediately if an SAE occurs.

Visit 3 (30 [+ 14] days after Visit 2): Collection of Safety Information and Blood Sample

1) Collect the diary card and review each page with the subject, including any AEs, medications, or therapy that occurred since vaccination.
2) Review the temporary contraindications for blood sampling (see Section 5.2.8).
3) Obtain the third blood sample (approximately 10 mL; see Section 7.1 for details regarding the collection of blood samples).
4) Complete the relevant CRFs for this visit and the End of Study CRF.
5) If the subject does not return for Visit 3, and the diary card is not received at the site, site personnel will contact the subject by telephone. During the telephone call, the subject 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 with 3 attempts, the study personnel will follow instructions given in Section 5.2.10.

5.1.4.3 Groups 5 and 6

Visit 1 (Day 0): Inclusion and Blood Sample

1) Explain the study objectives and design to the subject, including but not limited to its objectives, design, and risks and benefits, and answer any questions the subject may have.
2) Obtain a signed informed consent from the subject. The investigator or delegate will also sign and date the ICF, retain the original, and give a copy of the signed and dated form to the subject.
3) Check eligibility of the subject by reviewing applicable inclusion and exclusion criteria (see Section 5.2.4 and Section 5.2.5, respectively).
4) Collect subject number from Study MET44.
5) Collect relevant demographic data.
6) Obtain significant medical history (see Section 5.2.6 for details).
7) Perform a directed physical examination, if indicated, based on medical history.
8) Measure the temperature by the preferred route (see Section 9.3.2.3.2) and record this information in the source document. If the temperature is ≥ 100.4°F (38.0°C), defer enrollment until the subject is afebrile for at least 24 hours.
9) If the subject meets all inclusion and no exclusion criteria, connect to the IRT system for group assignment and allocation of subject number (see Section 6.5 for instructions).
10) Obtain the blood sample (approximately 10 mL; see Section 7.1 for details regarding the collection of blood samples). If attempts to obtain the blood draw are unsuccessful (3 attempts), then Visit 1 can be rescheduled to a later date at which point inclusion/exclusion criteria must be re-validated.
11) Observe the subject for 15 minutes following blood sampling for the occurrence of a syncopal episode.

12) Collect any SAEs related to study procedures.

13) Provide the subject with a memory aid to record any SAEs related to blood sampling for the first 3 days after Visit 1.

14) Remind the subject that they will be contacted by telephone on or about Day 8 post-Visit 1 to ask them about any SAEs that might be related to blood sampling.

15) Collect reportable concomitant medications (see Section 6.7).

16) Complete the relevant CRFs for this visit and the End of Study CRF.

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

Unless a subject 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 LVLS (last visit, last subject):
Q3 2019 to Q1 2022

Planned end of study: Q1 2022

Planned date of final clinical study report (CSR): 10 months after completion of Stage I

Planned date of CSR addendum: 10 months after completion of Stage II

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Subjects who received MenACYW conjugate vaccine or Menomune vaccine at least 3 years ago in Study MET49 or Study MET44 at age ≥ 56 years will be recruited for this study. The site will ensure that any advertisements used to recruit subjects (informational brochures, letters, pamphlets, posters, and other advertisements) are submitted to Sanofi Pasteur prior to submission to the IRB(s) for approval.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject voluntarily confirms 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 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.

The actual ICF used at each center may differ, depending on local regulations and 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 IRB prior to the form being used.

If new information becomes available that may be relevant to the subject's 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.

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) Received primary vaccination at ≥ 56 years of age with either Menomune vaccine or MenACYW conjugate vaccine, as assigned by randomization, in Study MET49 or Study MET44.[a]
2) Informed consent form has been signed and dated.
3) Able to attend all scheduled visits and to comply with all study 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 vaccination and until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, surgically sterile, or ≥ 60 years of age.

[a] "≥ 56 years" means from the day of the 56th birthday onwards.

2) Participation in the 4 weeks preceding study enrollment/vaccination or planned participation during the active phase of the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.

   Note: "Active phase" refers to the period of time from revaccination with MenACYW conjugate vaccine to the end of the short-term (i.e., ~30 days) follow-up after the vaccination. Accordingly, following the blood draw at Visit 1, subjects in Group 3 and Group 4 will have a 2-year inactive phase prior to Visit 2. Prior to Visit 2, subjects in Group 3 and Group 4 will have inclusion and exclusion criteria reassessed and will continue with or be excluded from further participation in the study as appropriate.

3) Receipt of any vaccine in the 4 weeks (28 days) preceding the study vaccination or planned receipt of any vaccine during the active phase of the present study except for influenza vaccination, which may be received at least 2 weeks before or after study vaccine. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

4) Receipt or planned receipt of any meningococcal vaccine since receipt of a single dose of MenACYW conjugate vaccine or Menomune vaccine in Study MET49 or Study MET44.

5) Receipt of immune globulins, blood, or blood-derived products in the 3 months prior to either enrollment or MenACYW conjugate vaccination in the current study.

6) 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 prior either to enrollment or MenACYW conjugate vaccination in the current study).

7) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically.

8) At high risk for meningococcal infection during the study (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).

9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the study or to a vaccine containing any of the same substances[a] (excluding subjects in Group 5 and Group 6).

10) Verbal report of thrombocytopenia, contraindicating IM vaccination, in the Investigator's opinion (excluding subjects in Group 5 and Group 6)

11) Personal history of GBS (excluding subjects in Group 5 and Group 6).

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 (excluding subjects in Group 5 and Group 6).

[a] The components of MenACYW conjugate vaccine are listed in Section 6.1 and in the Investigator's Brochure.

13) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion (excluding subjects in Group 5 and Group 6), contraindicating IM vaccination in the Investigator's opinion.
14) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.
15) Current alcohol abuse or drug addiction.
16) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion.[a]
17) 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 or receive study vaccination until the condition has resolved or the febrile event has subsided.
18) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw. A prospective subject should not be included in the study or receive study vaccination until 72 hours have elapsed since receipt of oral or injectable antibiotic therapy.
19) 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 (i.e., 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 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

[a] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases

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

Not applicable.

5.2.8 Contraindication for Subsequent Blood Samples

Should a subject receive oral or injectable antibiotic therapy within 3 days before the second or third 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 the 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.

5.2.9 Conditions for Withdrawal

Subjects will be informed that they have the right to withdraw 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, based on 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.

5.2.10 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (i.e., 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.

5.2.11 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 5.2.10. The certified letter was sent by the investigator and returned unsigned, and the subject 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 (e.g., 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 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	To be used: • When the subject indicated unwillingness to continue in the study. • When the subject made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., subject is relocating, inform consent withdrawal, etc.).

5.2.12 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 except if they specified that they do not want to be contacted again and it is documented in the source document.

5.2.13 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 and if the study vaccine has been

administered, the subject will not be discontinued from the study. 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. 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 (i.e., 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 (e.g., 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 RMOs for advice on how to address any study related medical question or problem. The RMOs will be available 24 hours a day, 7 days a week, as needed. Contact information for the RMOs 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 the GPV Department (please refer to Section 10).

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 (e.g., those that affect the conduct of the study or the safety of subjects) require 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. Administrative changes do not require IRB approval; however, the IRB must be notified whenever one is made.

The Investigator is responsible for ensuring that changes to an approved study, during the period for which IRB approval has already been given, are not initiated without 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 that warrant study discontinuation; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IRB(s), 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 IRB(s), 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 and should assure appropriate subject therapy and/or follow-up.

6 Vaccines Administered

6.1 Identity of the Investigational Product

MenACYW conjugate vaccine is composed of 4 distinct meningococcal capsular polysaccharides (serogroups A, C, W, and Y) from *N. meningitidis*, which are each covalently bound to tetanus toxoid protein prepared from cultures of *Clostridium tetani*. The final bulk of MenACYW conjugate vaccine is formulated from the 4 monovalent polysaccharide-protein conjugates and diluted in sodium acetate buffered saline solution to a final concentration of 10 µg polysaccharide/serogroup/0.5 mL.

MenACYW conjugate vaccine is manufactured at Sanofi Pasteur Inc., Swiftwater, Pennsylvania, USA. The purified meningococcal capsular polysaccharides used for the manufacturing of MenACYW conjugate vaccine are the same as those used for the manufacturing of the licensed vaccine, Menactra (and had been used for Menomune A/C/Y/W-135), manufactured at the same site. The tetanus toxoid protein used to prepare the polysaccharide-protein monovalent conjugate concentrates is manufactured at Sanofi Pasteur SA, Marcy l 'Etoile, France, and is derived from the licensed manufacturing process used for the preparation of the licensed ActHIB vaccine.

6.1.1 Identity of Study Product

MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate vaccine

6.1.1.1 Composition

Each 0.5 mL dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain 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]

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

6.1.1.2 Preparation and Administration

MenACYW conjugate vaccine is a liquid preparation; as such, no diluent is required. This product is provided in 0.5-mL single-dose vials. The vaccine will be administered intramuscularly into the deltoid muscle of the arm. The vaccine must be administered within 30 minutes of removing the vaccine from the refrigerator.

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; another dose is to be used, and the event is to be reported to the Sponsor.

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 in Groups 1 and 2 will receive 1 dose of MenACYW conjugate vaccine at Visit 1. All subjects in Groups 3 and 4 will receive 1 dose of MenACYW vaccine at Visit 2, 2 years after enrollment in the study.

6.1.2 Identity of Control Product

Not applicable.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

MenACYW conjugate vaccine will be supplied by the Sponsor in single-dose vials, labeled and packaged according to national regulations.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Clinical Logistics Coordinator 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 (i.e., 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 and should be protected from light. 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 study 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 study site, product inventory at the site, the dose 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 CRB. If applicable, information may also be entered into the subject's vaccination card.

The Sponsor's monitoring staff will verify the study 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 study, 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 (e.g., 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 decides to launch a retrieval procedure, the Investigators will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

Not applicable. This is an open-label study.

6.5 Randomization and Allocation Procedures

On the day of enrollment, a planned minimum of 440 subjects who meet all inclusion criteria and no exclusion criteria, sign the ICF, and who participated in Study MET49 will be randomly assigned in a 9:2 ratio to Group 1 (180 subjects) or Group 3 (40 subjects), or Group 2 (180 subjects) or Group 4 (40 subjects), depending on the vaccine originally received in Study MET49. A planned nonrandom subset (i.e., the first 60 subjects enrolled in Group 1 and the first 60 subjects enrolled in Group 2) will provide an additional blood sample 6 (window, 5 to 7) days post-vaccination. A planned total of 120 subjects who participated in Study MET44 and who meet all inclusion criteria and no exclusion criteria and sign the ICF will be assigned to Group 5 (60 subjects) or Group 6 (60 subjects), depending on the vaccine originally received in Study MET44.

Site staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data in response to IRT system prompts. The IRT system will then provide the group assignment and subject number and have the site staff confirm it. The full detailed procedures for using the IRT system are described in the Operating Guidelines. If the subject is not eligible to participate in the study, information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IRT system will consist of a 12-digit string (a 3-digit country code, 4-digit study center identifier and a 5-digit subject identifier). For example, Subject 840000100001 is the first subject enrolled in center number 1 in the United States

(840 being the US country code). Subject numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT system. To maximize the opportunity to achieve a 9:2 ratio (Group 1:Group 3 and Group 2:Group 4), randomization will not be performed at the site level, but across all sites.

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 and other therapies (e.g., blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions/AEs during study participation.

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of vaccination to the end of the solicited and unsolicited follow-up period (e.g., 30-day safety follow-up). For Groups 3, 4, 5, and 6 during Stage I, only information on systemic (oral or injectable) antibiotics will be collected in the CRB at Visit 1 prior to the blood draw.

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. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (e.g., antipyretics, analgesics, and non-steroidal anti-inflammatory drugs, steroids/corticosteroids).
- Category 2: medications impacting or that may have an impact on the immune response (e.g., other vaccines, blood products, steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Category 3: Systemic (oral or injectable) antibiotics, as they may interfere with bioassays used for antibody testing when taken before a blood draw.

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

- Trade name

- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables.
- Medication category (1, 2, or 3)
- Start and stop dates

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded.

Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance, not as a Category 2 medication.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected from subjects in Groups 1 and 2 at Visits 1 and 2 (or at Visits 1, 2, and 3 for those subjects included in the Day 6 subset); from subjects in Groups 3 and 4 at Visits 1, 2, and 3; and from subjects in Groups 5 and 6 at Visit 1. See the Tables of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

Blood sample collection by group is described in Section 5.1.3.

For each sample, approximately 10 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. 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 immune 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 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 up to a maximum of 24 hours. The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes. These tubes should be

pre-labeled with adhesive labels that identify the study code, the subject's number, and the sampling stage or visit number (see Section 5.1.3 and Section 7.1).

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 Global Clinical Immunology (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 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 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 endpoint for the evaluation of immunogenicity is:

Vaccine seroresponse to meningococcal serogroups A, C, W, and Y as measured by hSBA at baseline (D0, pre-vaccination) and 30 (window, +14) days after vaccination in Group 1 (Menomune-primed) subjects.

The definition of seroresponse is presented in Section 12.1.1.

9.1.1.2 Immunogenicity Assessment Methods

Antibodies to Meningococcal Antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, W, and Y will be measured in an hSBA. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with human complement are added to the serum dilutions and allowed to incubate. After this incubation period, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight at 37°C with 5% 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 quantification (LLOQ) of the hSBA assay is a titer of 1:4.

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:

- Vaccine seroresponse to meningococcal serogroups A, C, W, and Y as measured by hSBA at baseline (D0, pre-vaccination) and 30 (window, +14) days after vaccination in Group 2 (MenACYW conjugate vaccine-primed) subjects.
- Vaccine seroresponse 6 (window, 5–7) days after vaccination as measured by hSBA in approximately 60 subjects from Group 1 and approximately 60 subjects from Group 2.

The definition of seroresponse is presented in Section 12.1.2.1.

- During Stage I, antibody persistence after primary vaccination with Menomune vaccine or MenACYW conjugate vaccine as measured by hSBA and rSBA will be evaluated at Day 0 in Groups 1-4 (3 years after primary vaccination in Study MET49) and in Groups 5 and 6 (6-7 years after primary vaccination in Study MET44). Two years later, during Stage II, antibody persistence will be evaluated again in Groups 3 and 4 (5 years after primary vaccination in Study MET49).

9.2.1.2 Immunogenicity Assessment Methods

Antibodies to Meningococcal Antigens (hSBA Method)

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

Antibodies to Meningococcal Antigens (rSBA Method)

Functional meningococcal antibody activity against serogroups A, C, W, and Y will be measured in an rSBA. 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 µL of the serum/complement/bacteria mixture is removed and added to a blood agar plate using the tilt method, and then incubated overnight at 37°C with 5% CO_2. Bacterial colonies present on the blood agar plate are then counted.

The bactericidal titer of each sample is expressed as the final reciprocal dilution yielding ≥ 50% killing as compared to the T60 (average number of bacteria in each control well after incubation) colony-forming unit. The LLOQ for this assay is a titer of 1:4.

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

Antibody titers (hSBA and rSBA) will be measured for each meningococcal serogroup for the following groups of subjects:

- For all subjects on Day 0
- For a subset of subjects in Groups 1 and 2, on Day 6 (window, Days 5–7) following vaccination
- For subjects in Group 3 and 4, on Day 0 + 2 years
- For all subjects who receive a single dose of MenACYW conjugate vaccine, 30 (window, + 14) days following vaccination

Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested to assess:

- Antibody concentrations against tetanus toxoid at Day 0 (all groups), 2 years after enrollment (Groups 3 and 4), and 30 (window, + 14) days after the administration of a single dose of MenACYW conjugate vaccine in Study MEQ00066 (Groups 1-4)

9.3.1.2 Immunogenicity Assessment Methods

Antibodies to Meningococcal Antigens (hSBA Method)

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

Antibodies to Meningococcal Antigens (rSBA Method)

The immunogenicity assessment method for the observational endpoints for rSBA is the same as that presented in Section 9.2.1.2.

Antibodies to Tetanus Toxin

Anti-tetanus antibodies will be measured by electrochemiluminescence (ECL).

The Diphtheria, Tetanus, and Pertussis ECL is a multiplexed serological assay which allows for the simultaneous quantification of human antibodies to 6 specific antigens including diphtheria toxoid, tetanus toxoid, and 4 pertussis antigens: pertussis toxin, filamentous haemagglutinin, fimbriae and pertactin.

In this assay, each well of a 96-well microtiter plate is pre-coated in precise positions with the 6 different antigens in a multi-spot fashion. Following incubation with serum samples, antigen specific antibodies bind to the respective antigens. The captured antibodies are then detected using a sulfotag-conjugated anti-human IgG conjugate. Electrical stimulation of the conjugate in the presence of a chemiluminescent substrate results in the generation of a light signal from each specific spot that is captured by a camera in relative light units. The signal generated is directly proportional to the amount of antibodies present in the sample, which is quantified using software and based on an established reference standard sample curve. For this study, only tetanus results will be calculated.

9.3.2 Safety

9.3.2.1 Safety Definitions

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

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

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

Adverse Reaction:

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

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

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or outpatient treatment with no hospitalization.

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

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

Solicited Reaction:

A solicited reaction is an "expected" AR (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (e.g., injection site pain or headache occurring between Day 0 and Day 7 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.

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 Day 0 and Day 7 is a solicited reaction (i.e., prelisted in the protocol and CRB), then a headache starting on Day 7 is a solicited reaction, whereas headache starting on Day 8 post-vaccination is an unsolicited AE. Unsolicited AEs include both SAEs and non-serious unsolicited AEs.

Medically Attended AE (MAAE)

An MAAE is a new onset or a worsening of a condition that prompts the subject to seek unplanned medical advice at a physician's office or emergency department. A physician contact made over the phone or by email will be considered a physician office visit for the purpose of MAAE collection. This definition excludes pre-planned medical office visits for routine medical care, as well as follow-up visits of chronic conditions with an onset prior to entry in the study. An AE discovered during a planned routine visit (e.g., upper respiratory tract infection, otitis) will be collected as an MAAE.

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

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

9.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) injection site reactions occurring from Day 0 through Day 7 after vaccination.
- Occurrence, time to 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 from Day 0 through Day 7 after vaccination.
- Occurrence, nature (MedDRA preferred term), time to 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 occurring from Day 0 through ~Day 30 after vaccination. MAAEs will be collected as unsolicited non-serious AEs from Day 0 through ~Day 30 after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs, including AESIs, throughout the study.

9.3.2.3 Safety Assessment Methods

At each visit, the Investigator or a delegate will perform a directed physical examination, if indicated, based on interim history and will ask the subject 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 Observation Period

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

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected).
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination.

- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10.

9.3.2.3.2 Reactogenicity (Solicited Reactions From Day 0 Through Day 7 After Vaccination)

After vaccination, subjects in Groups 1 to 4 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 in the diary card on the day of vaccination and for the next 7 days (i.e., 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 (e.g., medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

Subjects 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[a]	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

[a] For the subjective reaction of pain, subjects 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

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[a]	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.

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

9.3.2.3.3 Unsolicited Adverse Events

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

Information on SAEs will be collected and assessed throughout the study, from inclusion until 30 days after vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., 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 AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

[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 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.3.2.3.5.

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

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- Whether the AE was serious

  For each SAE, the investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)

- Whether the AE caused study discontinuation

9.3.2.3.4 Adverse Events of Special Interest

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

- Generalized seizures (febrile and non-febrile) (19) (20)
- Kawasaki disease (21) (22) (23)
- Guillain-Barré syndrome (24)
- Idiopathic thrombocytopenic purpura (25) (26)

These events have been listed as AESIs based on the feedback received from the European Union regulators for other studies (conducted in younger age groups). No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in 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.

9.3.2.3.5 Assessment of Causality

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

Not related – The AE is clearly/most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the 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 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 products. It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, autopsy report) 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 [MD or DO]) 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 MTLs 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 one of the following means:

- By fax, to the following number: 1-570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
- By express mail, to the following address:
  Sanofi Pasteur, Inc.
  Reception & Triage – Case Management
  Global Pharmacovigilance Department
  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 RMOs 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 (e.g., 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 (e.g., 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, other products (e.g., 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 9.3.2.3.5.

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 Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs/IRBs

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

The Sponsor's RMOs will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators/Sponsor will be responsible for informing the IRB(s) that reviewed the study protocol.

11 Data Collection and Management

11.1 Data Collection and CRF 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 as described in Section 9.3.2.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Subjects 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 on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the subjects 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 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 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(s). 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

A 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 in a blinded manner. Periodic safety data review will be performed by the Sponsor's Safety Management Team.

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 statistical analyses are conducted. In accordance with the protocol, the SAP will describe all analyses to be performed under the responsibility of the Sponsor and all the conventions to be taken.

Summaries of baseline demographic characteristics of the study subjects will be presented. The number of subjects enrolled and their age at enrollment, sex, race, and ethnic origin will be summarized for each group, as well as the number and description of protocol deviations.

Categorical variables will be summarized and presented by frequency counts, percentages and 95% confidence intervals (CIs). Continuous variables will be summarized and presented with means, standard deviations, and 95% 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 the normal approximation assuming they are log-normally distributed.

12.1.1 Hypothesis and Statistical Methods for the Primary Objective

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

Vaccine seroresponse will be considered sufficient if the lower limit of the 1-sided 97.5% CI for the percentage of subjects with an hSBA vaccine seroresponse against serogroups A, C, W and Y is greater than 40%.

This is equivalent to testing H0: $p \leq 0.40$ against H1: $p > 0.40$, where p is the observed proportion of subjects with hSBA vaccine seroresponse against serogroups A, C, W and Y. The 1-sided 97.5% CI for the single proportion will be calculated using the exact method (Clopper-Pearson method).

*hSBA vaccine seroresponse for serogroups A, C, W, and Y 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

12.1.2.1 Secondary Objective 1

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

Vaccine seroresponse will be considered sufficient if the lower limit of the 1-sided 97.5% CI for the percentage of subjects with an hSBA vaccine seroresponse against serogroups A, C, W and Y is greater than 40%.

This is equivalent to testing H0: $p \leq 0.40$ against H1: $p > 0.40$, where p is the observed proportion of subjects with hSBA vaccine seroresponse against serogroups A, C, W and Y. The 1 sided 97.5% CI for the single proportion will be calculated using the exact method (Clopper-Pearson method).

*hSBA vaccine seroresponse for serogroups A, C, W, and Y 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.

12.1.2.2 Secondary Objective 2

No hypotheses will be tested.

The proportions of subjects in a planned nonrandom subset (approximately 60 subjects from Group 1 and approximately 60 subjects from Group 2) with vaccine seroresponse for meningococcal serogroups A, C, W, and Y at 6 (window, 5–7) days following vaccination will be determined; 95% CIs of point estimates will be calculated assuming proportions follow a binomial distribution using the Exact method.

12.1.2.3 Secondary Objective 3

No hypotheses will be tested.

For GMTs, the 95% CIs of point estimates will be calculated using the normal approximation assuming antibody titers/concentrations are log normally distributed. For proportions, 95% CIs of point estimates will be calculated assuming proportions follow a binomial distribution using the Exact method.

Categorical variables will be summarized and presented by frequency counts, proportion 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.

RCDC figures and kinetic curves will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine.

Descriptive analyses on A, C, W, and Y serogroups will include:

- hSBA and rSBA GMTs and corresponding 95% CIs
- hSBA and rSBA titer distribution and RCDCs
- Percentages of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and corresponding 95% CIs
- Percentages of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 and corresponding 95% CIs

12.1.3 Statistical Methods for Observational Objectives

Immunogenicity

All analyses will be descriptive; no hypotheses will be tested.

For GMTs and geometric mean concentrations (GMCs), 95% CIs of point estimates will be calculated using the normal approximation assuming antibody titers/concentrations are log normally distributed. For proportions, 95% CIs of point estimates will be calculated assuming proportions follow a binomial distribution using the Exact method.

Descriptive analyses on A, C, W, and Y serogroups will include:

- hSBA and rSBA GMTs and corresponding 95% CIs
- hSBA and rSBA titer distribution and RCDCs
- Percentages of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and corresponding 95% CIs
- Percentages of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 and corresponding 95% CIs
- Proportion with at least a 4-fold increase in hSBA and rSBA antibody titer compared to baseline (Group 1 and Group 2 during Stage I and Group 3 and Group 4 during Stage II)
  - An hSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as a post-vaccination titer ≥ 1:16 for subjects with pre-vaccination titer < 1:8, or a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with a pre-vaccination titer ≥ 1:8.
  - An 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.
- Ratio of the GMT post-vaccination/GMT pre-vaccination and the associated 95% CI of the ratio (at Day 30 for Group 1 and Group 2 and at Day 6 in a subset of Group 1 and Group 2 [during Stage I], and at Day 30 for Group 3 and Group 4 [during Stage II]).

Descriptive analyses on anti-tetanus antibody concentrations will include:

- Geometric mean concentrations at Day 0 (all groups), 2 years after enrollment (Groups 3 and 4), and 30 (window, + 14) days after the administration of a single dose of MenACYW conjugate vaccine in Study MEQ00066 (Groups 1–4)
- Proportion of subjects achieving seroprotective antibody levels ≥ 0.01 IU (international units) /mL, ≥ 0.1 IU/mL, and ≥ 1.0 IU/mL to tetanus toxoid 30 (window, + 14) days after the

administration of a single dose of MenACYW conjugate vaccine in Study MEQ00066 (Groups 1–4)

- RCDCs and kinetic curves

Safety

All analyses will be descriptive; no hypotheses will be tested.

Safety results will be described for subjects revaccinated with MenACYW conjugate vaccine (i.e., Groups 1–4). The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method).

The frequency and percentage of subjects who had solicited injection site and systemic reactions and their 95% CIs will be provided. These events will be tabulated by type of reactions and intensity for each study group. These events will also be summarized by other categories specified in the endpoints (e.g., time of onset, number of days of occurrence, action taken).

Unsolicited AEs will be collected, coded, and summarized by MedDRA system organ class and PT. For each unsolicited AE, the number of subjects with at least one instance of that event will be reported. Unsolicited AEs will also be tabulated by intensity and relatedness of study vaccine and by other categories specified in the endpoints.

Immediate reactions, SAEs, and any event that leads to subject withdrawal from the study will be tabulated separately.

12.2 Analysis Sets

12.2.1 Stage I Analysis Sets

12.2.1.1 Full Analysis Sets

The Stage I Day 30 Full Analysis Set (FAS1) is defined as subjects in Groups 1 and 2 who received the study vaccine and have a valid serology result for at least 1 serogroup from a blood sample provided 30 (window, +14) days post-vaccination.

The Stage I Day 6 FAS (FAS2) is defined as the subset of Group 1 and 2 subjects who received the study vaccine and have a valid serology result for at least 1 serogroup from a blood sample provided 6 (window, 5–7) days post-vaccination.

The Stage I FAS for persistence (FAS3) includes subjects in Groups 1, 2, 3, 4, 5 and 6 who have a valid serology result for at least 1 serogroup from a pre-vaccination blood sample (3-year or 6–7-year antibody persistence).

12.2.1.2 Per-Protocol Analysis Sets

12.2.1.2.1 Day 30 Per-Protocol Analysis Set
Groups 1 and 2

The Stage I Day 30 Per-Protocol Analysis Set (PPAS1) is a subset of Stage I Day 30 FAS (FAS1). Subjects with at least 1 of the following relevant protocol deviations will be excluded from the PPAS1:

- Subject did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria
- Subject did not receive MenACYW conjugate vaccine according to randomization
- 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 pre-specified time window at 30 (window, + 14) days post-vaccination
- Subject received a protocol-prohibited therapy/medication/vaccine that might impact antibody response to the study vaccine
- Subjects received study vaccine deemed unacceptable for use (e.g., because of a temperature excursion).
- Subject's post-vaccination serology sample did not produce a valid test result for any antigen (i.e., results for all antigens are missing)
- Any other deviation identified during conduct of the study and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity

12.2.1.2.2 Day 6 Per-Protocol Analysis Set
Groups 1 and 2

The Day 6 PPAS (PPAS2) is a subset of Day 6 FAS (FAS2). Subjects with at least 1 of the following relevant protocol deviations will be excluded from the Day 6 PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria
- Subject did not receive MenACYW conjugate vaccine according to randomization
- 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 pre-specified time window at 6 (window, 5 to 7) days post-vaccination
- Subject received a protocol-prohibited therapy/medication/vaccine that might impact antibody response to the study vaccine

- Subjects received study vaccine deemed unacceptable for use (e.g., because of a temperature excursion).
- Subject's post-vaccination serology sample did not produce a valid test result for any antigen (i.e., results for all antigens are missing)
- Any other deviation identified during conduct of the study and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity

12.2.1.3 Safety Analysis Set
Groups 1 and 2

The Stage I Safety Analysis Set (SafAS1) is defined as those subjects who have received the study vaccine and have any safety data available. Safety will be analyzed according to the vaccine actually received by the subject.

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

12.2.2 Stage II Analysis Sets
Groups 3 and 4

12.2.2.1 Full Analysis Sets

The Stage II Day 30 FAS (FAS4) is defined as subjects in Groups 3 and 4 who received the study vaccine and have a valid serology result for at least 1 serogroup from a blood sample provided 30 (window, +14) days post-vaccination.

The Stage II FAS for persistence (FAS5) includes subjects in Groups 3 and 4 who have a valid serology result for at least 1 serogroup from a pre-vaccination blood sample (5-year antibody persistence).

12.2.2.2 Day 30 Per-Protocol Analysis Set

The Stage II Day 30 PPAS (PPAS3) is a subset of the Stage II Day 30 FAS (FAS4). Subjects with at least 1 of the following relevant protocol deviations will be excluded from the Stage II Day 30 PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria
- Subject did not receive MenACYW conjugate vaccine according to randomization
- 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 pre-specified time window at 30 (window, + 14) days post-vaccination

- Subject received a protocol-prohibited therapy/medication/vaccine that might impact antibody response to the study vaccine
- Subjects received study vaccine deemed unacceptable for use (e.g., because of a temperature excursion).
- Subject's post-vaccination serology sample did not produce a valid test result for any antigen (i.e., results for all antigens are missing)
- Any other deviation identified during conduct of the study and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity

12.2.2.3 Safety Analysis Set

The Stage II Safety Analysis Set (SafAS2) is defined as those subjects who have received the study vaccine and have any safety data available. Safety will be analyzed according to the vaccine actually received by the subject.

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

12.2.3 Populations Used in Analyses

12.2.3.1 Stage I

The primary immunogenicity analyses will be performed on the Stage I Day 30 PPAS (PPAS1) and will be confirmed on the Stage I Day 30 FAS (FAS1). In the FAS1, subjects will be analyzed by the vaccine group to which they were randomized.

The secondary immunogenicity analyses (Day 6 subset) will be performed on the Day 6 PPAS (PPAS2) and Day 6 FAS (FAS2).

The secondary antibody persistence analyses will be performed on the FAS3.

The safety analysis will be performed on the Stage I Safety Analysis Set (SafAS1). Subjects will be analyzed according to the vaccine they actually received.

12.2.3.2 Stage II

Immunogenicity analyses will be performed on Stage II Day 30 PPAS (PPAS3) and confirmed on the Stage II Day 30 FAS (FAS4).

The secondary antibody persistence analyses will be performed on FAS5.

The safety analysis will be performed on the Stage II Safety Analysis Set (SafAS2). Subjects will be analyzed according to the vaccine they actually received.

12.3 Handling of Missing Data and Outliers

12.3.1 Immunogenicity

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

For the computations, LLOQ and upper limit of quantification (ULOQ) will be managed as follows:

- If a titer is < LLOQ, then LLOQ/2 will be used
- If a titer is ≥ LLOQ and < ULOQ, then the titer itself will be used
- If a titer is ≥ ULOQ, then ULOQ will be used

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

Relevant analyses will be completed for subjects in Groups 1, 2, 3, 4, 5, and 6 after completion of Stage I. After collecting all planned data for Groups 1, 2, 3, 4, 5, and 6 after completion of Stage I, the study database will be cleaned and locked. All statistical analyses planned for these groups will be conducted, and a final study report will be written.

After the post-revaccination safety and immunogenicity data for Group 3 and Group 4 are collected during Stage II, the database will be updated to include the newly collected data, which will be cleaned, and the database will be relocked. Analysis of the new data will be conducted and an addendum to the CSR will be written.

12.5 Determination of Sample Size and Power Calculation

A total of 560 subjects are planned to be enrolled:

- Group 1 (subjects who received Menomune vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine at enrollment in Study MEQ00066: n=180
- Group 2 (subjects who received MenACYW conjugate vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine at enrollment in Study MEQ00066: n=180
- Group 3 (subjects who received Menomune vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine 2 years after enrollment in Study MEQ00066: n=40
- Group 4 (subjects who received MenACYW conjugate vaccine in Study MET49) will receive a single dose of MenACYW conjugate vaccine 2 years after enrollment in Study MEQ00066: n =40
- Group 5 (subjects who previously received Menomune vaccine in Study MET44): n=60
- Group 6 (subjects who previously received MenACYW conjugate vaccine in Study MET44): n=60

For the Primary Objective and Secondary Objective 1: For Group 1 and Group 2, a sample size of 120 achieves at least 90.0% power to detect that the lower bound of the one-sided 97.5% CI is greater than 0.40 (proportion under the null hypothesis) using a 1-sided exact test with a significance level (alpha) of 0.025.

For all other groups (i.e., Groups 3–6), descriptive statistics will be calculated and presented in this study; hence, no sample size or study power was calculated for these groups.

13 Ethical and Legal Issues and Investigator/Sponsor Responsibilities

13.1 Ethical Conduct of the Study/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 study, 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, Data Protection, 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.

Each subject's race and ethnicity will be collected in this study because these data are required by regulatory agencies (e.g., on the African American population for the Food and Drug Administration or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan) (29).

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 members, and by inspectors from regulatory authorities.

[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.

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.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the study (i.e., before the inclusion of the first subject in 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 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 (e.g., 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 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 planned addendum to 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 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 study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives

recognition to the study 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 study 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 study are not to be considered confidential.

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

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15 Signature Page

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