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

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

Clinical Study Protocol

NCT Number: NCT04143061

WHO Universal Trial Number (UTN):	U1111-1183-6581
Study Code:	MET55
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:	MenACYW conjugate vaccine administered as a single dose to healthy adults, adolescents, and children in India and healthy adolescents and children in the Republic of South Africa
Manufacturer:	Same as Sponsor
Investigators:	This is a multi-center study with multiple Investigators. Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Sponsor's Responsible Medical Officer:	[redacted], MD Clinical Team Leader [redacted], Clinical Research and Development Shantha Biotechnics Pvt. Ltd. (a Sanofi Company) Vasantha Chambers 3rd and 4th Floor, Fatehmaidan Road, Basheerbagh, Hyderabad 500004, India Tel: [redacted] E-mail: [redacted]
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Version and Date of the Protocol: Version 2.0 dated 11 June 2019

History of Protocol Versions

Version	Date	Comments
1.0	20 August 2018	IRB/IEC submitted version not used in the study

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Synopsis

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

Title of the Study:	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Healthy Adults, Adolescents, and Children in India and Healthy Adolescents and Children in the Republic of South Africa
Development Phase:	Phase III
Investigators:	This will be a multi-center study with multiple Investigators.
Study Centers:	This will be a multi-center study conducted at approximately 12 sites in India and 7 sites in the Republic of South Africa (RSA). Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	4Q 2019 to 1Q 2021
Study Design and Methodology:	This will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, step-wise, multi-center study to compare and describe the immunogenicity and safety of MenACYW conjugate vaccine when administered as a single dose in healthy adults, adolescents, and children in India and a modified double-blind, randomized, parallel-group, active-controlled, multi-center study to compare and describe the immunogenicity and safety of MenACYW conjugate vaccine when administered as a single dose in healthy adolescents and children in RSA. Approximately 866 healthy adults, adolescents, and children will be assigned into 1 of 3 cohorts and randomized 1:1 to the following groups within those cohorts in India: **Cohort Ia** (Adults aged 18 to 55 years; 200 subjects; 1 vaccination): • Group (Gr) 1 (MenACYW conjugate vaccine) • Gr 2 (Menactra®) **Cohort Ib** (Adults aged ≥ 56 years; 200 subjects; 1 vaccination): • Gr 3 (MenACYW conjugate vaccine) • Gr 4 (Quadri Meningo™ or any locally available licensed meningococcal vaccine) **Cohort II** (Children and Adolescents aged 2 to 17 years; 466 subjects; 1 vaccination): • Gr 5 (MenACYW conjugate vaccine) • Gr 6 (Menactra®) Approximately 466 healthy adolescents and children aged 2 to 17 years will be randomized 1:1 to the following groups in RSA: • Gr7 (MenACYW conjugate vaccine) • Gr 8 (Menactra®)

	The recruitment in ages 2 to 17 years will be stratified to ensure an equal distribution into 2 subgroups (2 to 9 years and 10 to 17 years) in both of the countries. This will be done to ensure distribution of subjects across the complete age range. As an expectation of the regulatory agencies in India, it is proposed that this study will only use a step-wise approach for enrollment in India. Enrollment of Cohorts Ia (adults 18 to 55 years of age) and Ib (adults 56 years of age and older) will take place simultaneously. Enrollment of Cohort II will be initiated once the safety data collected from Day (D) 0 to D07 post-vaccination in a subset of first 100 subjects in adult Cohorts Ia and Ib (approximately first 10 subjects from each of the 12 sites across both cohorts) have been reviewed. This Early Safety Data Review (ESDR) to assess whether proceeding to the younger age cohort (children and adolescents) in India is appropriate, will first be done by the Sponsor's Safety Management Team (SMT) and subsequently by an independent Data Safety Monitoring Board (DSMB) that will be established for independent safety oversight of this study. RSA will not use a step-wise approach to enrollment and will enroll children and adolescents independent of India's ESDR design. The safety of the investigational product will also be continuously monitored by the Sponsor throughout the study. Periodic safety data review will be performed by the Sponsor's SMT. For all safety reviews, blinded safety data will be provided to the Sponsor's SMT. A formal additional DSMB review is also proposed following completion of the study. All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and 30 to 44 days post-vaccination. For subjects in Groups 7 and 8 (ie, RSA only), Human Immunodeficiency Virus (HIV) testing will additionally be performed at baseline if the consent is received. Safety data will be collected as follows: Immediate unsolicited systemic adverse events (AEs) will be collected within 30 minutes after vaccination. Solicited AE information will be collected from D0 to D07 after vaccination; unsolicited AE information will be collected from D0 to Visit (V) 02 after vaccination, and serious adverse event (SAE) information (including adverse events of special interest [AESIs]) will be collected throughout the study.
Early Safety Data Review:	The safety of the investigational product will be continuously monitored by the Sponsor. In India, ESDR will be performed, the goal of which is to allow for a cautious, step-wise approach to vaccine administration in order to comply with regulatory expectations. An initial safety review for this study is planned when a subset (100 subjects across both cohorts) of subjects from Cohorts Ia and Ib have been vaccinated and have provided safety data for D0 to D07 post-vaccination, using the data collection methods described in the protocol. The safety data collected will be entered into the case report books (CRBs), and will be summarized and reviewed by the Sponsor, initially in a blinded manner. It is understood that this review is based on preliminary data that have not been subject to validation and database lock. The following safety parameters will be assessed as part of the early safety review: • Immediate reactions • Solicited injection site and systemic reactions • Unsolicited AEs reported as related by the Investigator

	• SAEs (including AESIs) The data will be examined for the following alert thresholds defined for this study: • Any deaths, regardless of causality • Any vaccine-related SAEs • Grade 3 fever reported in more than 5% of subjects If any of the above criteria are met at the time of the ESDR, a decision will be made as to whether enrollment in the study will be allowed to resume. While safety for the specific cohort is reviewed, and until "go" decision is obtained by the internal SMT and independent DSMB, enrollment in the next cohort will not proceed. In addition, the option of partial or full unblinding is available to the Sponsor through the appointment of an independent statistician, if required, for a further in-depth review of the data. Apart from the early safety review, the study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), or the governing regulatory authorities in the countries where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigators shall inform their respective IEC/IRB. The Investigators shall also promptly inform the study subjects /subjects' parents / legally acceptable representatives (LARs) and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	To demonstrate the non-inferiority of immunogenicity of a single dose of MenACYW conjugate vaccine compared to Menactra® in adolescents and children aged 2 to 17 years in terms of serum bactericidal assay using human complement (hSBA) titers in India and RSA.
Primary Endpoint:	hSBA antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and at D30 (+14 days) after vaccination in adolescents and children aged 2 to 17 years in India and RSA ([Gr 5 + Gr 7] versus [Gr 6 + Gr 8])

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

Secondary Endpoints:	1) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and serum bactericidal assay using baby rabbit complement (rSBA) (in a subset)* before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in adults aged 18 to 55 years in India (Gr 1 versus Gr 2) 2) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset) * before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years in India (Gr 3 versus Gr 4) 3) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset) * before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India and RSA ([Gr 5 + Gr 7] versus [Gr 6 + Gr 8]) 4) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset) * before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India (Gr 5 versus Gr 6) 5) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset) * before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in RSA (Gr 7 versus Gr 8) * rSBA data will be generated in a subset of subjects as follows: • Groups 1, 2, 3, and 4: 50 subjects each • Groups 5, 6, 7, and 8: 100 subjects each
Observational Objectives:	***Immunogenicity*** 1) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in the children and adolescents aged 2 to 17 years by age groups (2 to 9 years of age and 10 to 17 years of age) in India and RSA combined and separated by India only or RSA only ***Safety*** 1) To describe the safety profile of MenACYW conjugate vaccine and that of licensed Menactra® in adults aged 18 to 55 years in India 2) To describe the safety profile of MenACYW conjugate vaccine and that of licensed Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years in India 3) To describe the safety profile of MenACYW conjugate vaccine and that of licensed Menactra® in children and adolescents aged 2 to 17 years in India and RSA

Observational Endpoints:	***Immunogenicity*** Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset) before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years by age groups (2 to 9 years of age and 10 to 17 years of age)
	Safety These endpoints are for all the safety objectives. • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) injection site reactions occurring up to D07 after vaccination. • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to D07 after vaccination. • Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to D30 after vaccination. • Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the study.
Planned Sample Size:	Approximately 1332 subjects are planned to be enrolled (with an estimated drop-out rate of 15% [calculated for age groups 2 - 17 years only]): 200 adults aged 18 to 55 years, 200 adults aged ≥ 56 years, and 932 children and adolescents aged 2 to 17 years (stratified as 466 subjects aged 2 to 9 years and 466 subjects aged 10 to 17 years). **Cohort Ia** (Adults aged 18 to 55 years in India): • Gr 1 (MenACYW conjugate vaccine): n = 100 • Gr 2 (Menactra®): n = 100 **Cohort Ib** (Adults aged ≥ 56 years in India): • Gr 3 (MenACYW conjugate vaccine) n = 100 • Gr 4 (Quadri Meningo™ or any locally available licensed meningococcal vaccine) n = 100 **Cohort II** (Children and Adolescents aged 2 to 17 years in India and RSA): ***India*** • Gr 5 (MenACYW conjugate vaccine): n = 233 • Gr 6 (Menactra®): n = 233

	RSA Children and Adolescents aged 2 to 17 years: • Group 7 (MenACYW conjugate vaccine): n = 233 • Group 8 (Menactra®): n = 233
Schedule of Study Procedures:	Vaccination **Cohorts Ia, and Ib (in India):** Subjects in Groups 1 and 3 will receive 1 dose of MenACYW conjugate vaccine on D0. Subjects in Gr 2 will receive 1 dose of Menactra® on D0. Subjects in Gr 4 will receive 1 dose of Quadri Meningo™ (or any locally available licensed meningococcal vaccine) on D0. **Cohort II (in India and RSA):** ***India*** Subjects in Gr 5 will receive 1 dose of MenACYW conjugate vaccine on D0. Subjects in Gr 6 will receive 1 dose of Menactra® on D0. ***RSA*** Subjects in Gr 7 will receive 1 dose of MenACYW conjugate vaccine on D0. Subjects in Gr 8 will receive 1 dose of Menactra® on D0. Blood Sampling All subjects will have 2 blood draws. These subjects will provide a pre-vaccination blood sample at V01 and a post-vaccination sample at V02 (30 to 44 days after vaccination on D0). Collection of Safety Data • All subjects will be followed for safety from V01 to V02 after vaccination • All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the CRB. • The subject or the subject's parent / LAR will record information in a diary card about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to V02 after vaccination. • SAEs (including AESIs) will be recorded throughout the duration of the study. • The subject or the subject's parent / LAR will be asked to notify the site immediately about any potential SAEs at any time during the study. • Staff will contact the subject or the subject's parent / LAR on D03 (+2 days) (for Cohorts Ia and Ib) and on D08 (+2 days) (for Cohort II) after vaccination to identify the occurrence of any SAE (including AESIs) that have not been reported, and to remind them to complete the diary card and to bring it back at the next visit. • The completed diary card will be reviewed with the subject or the subject's parent / LAR at V02

Duration of Participation in the Study:	The duration of each subject's participation in the study will be approximately 31 to 45 days.
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 milliliters (mL) dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients: Meningococcal capsular polysaccharides: Serogroup A..... 10 micrograms (µg) Serogroup C.....10 µg Serogroup Y.....10 µg Serogroup W.....10 µg Tetanus toxoid protein carrier..... approximately 55 µg* * Tetanus toxoid protein quantity is approximate and dependent on the PS-to-protein ratio for the conjugates used in each formulation.
Route:	IM
Batch Number:	To be determined
Control Product 1:	**Menactra®:** Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur Inc, Swiftwater, PA, USA)
Form:	Sterile aqueous solution
Composition:	Each 0.5 mL dose of Menactra® is formulated to contain the following ingredients: Meningococcal (serogroup A) polysaccharide (monovalent conjugate) .....4 µg Meningococcal (serogroup C) polysaccharide (monovalent conjugate) .....4 µg Meningococcal (serogroup Y) polysaccharide (monovalent conjugate) .....4 µg Meningococcal (serogroup W-135) polysaccharide (monovalent conjugate) .....4 µg Diphtheria toxoid protein (carrier protein).....48 µg* Sodium chloride (excipient).....4.35 mg Sodium phosphate (excipient) .....0.7 mg *Diphtheria toxoid quantity is approximate and dependent on the conjugate polysaccharide to protein ratio
Route:	IM
Batch Number:	To be determined

Control Product 2:	**Quadri Meningo™ (MenPS A,C,Y & W135):** Meningococcal Polysaccharide Vaccine (Group A, C, Y & W135) (Bio-Med Pvt. Ltd., Uttar Pradesh, India) or any locally available licensed meningococcal vaccine indicated for the age will be used
Form:	Lyophilisate for reconstitution with diluent to yield a solution for injection
Composition:	Each 0.5 mL dose is formulated to contain the following ingredients: Purified polysaccharide of *Neisseria meningitidis (N. meningitidis)* Group A .....50 µg Purified polysaccharide of *N. meningitidis* Group C .....50 µg Purified polysaccharide of *N. meningitidis* Group Y .....50 µg Purified polysaccharide of *N. meningitidis* Group W135 .....50 µg Lactose (I.P.) (stabilizer) .....5 mg Thimerosal (I.P.) (preservative).....0.05 mg
Route:	IM
Batch Number:	To be determined
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for study enrollment: **1) Age in the defined range on the day of inclusion** **For Adults:** Aged ≥ 18 years on the day of inclusion **For Children and Adolescents:** Aged 2 to 17 years on the day of inclusion **2) Z-score of ≥ -2 SD on the Weight-for-height table of the World Health Organization (WHO) Child Growth Standards** **For Children**: Children aged 2 to 5 years must have a Z-score of ≥ -2 SD on the Weight-for-height table of the WHO Child Growth Standards **3) Informed consent obtained** **For Adults**: Informed Consent Form has been signed and dated by the subject and by an independent witness, if required by local regulations **For Children and Adolescents**: Assent Form has been signed and dated by the subject (for subjects 7 to 17 years of age), and Informed Consent Form has been signed and dated by the parent(s) or legally acceptable representative and by an independent witness, if required by local regulations **4) Able to attend all scheduled visits and to comply with all study procedures** **For Adults**: Able to attend all scheduled visits and to comply with all study procedures **For Children and Adolescents**: Subjects and parent / legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

Exclusion Criteria for Adults, Adolescents, and Children:	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 until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be pre-menarche, or post-menopausal for at least 1 year, or surgically sterile 2) Participation at the time of study enrollment (or in the 4 weeks preceding the study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure 3) Receipt of any vaccine in the 4 weeks (28 days) preceding the study vaccination or planned receipt of any vaccine in the 4 weeks following vaccination except for oral poliovirus vaccine (OPV) in India, received during national immunization days. In India, OPV may be received with a gap of at least 2 weeks before the study vaccine. This exception includes monovalent and bivalent OPV. 4) Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C,Y, or W; or meningococcal B serogroup containing vaccine) 5) Receipt of immune globulins, blood or blood-derived products in the past 3 months 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) *Note: Subjects in Republic of South Africa (ie, Groups 7 and 8) will be included regardless of the HIV test results 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 traveling to countries with high endemic or epidemic disease) 9) Known systemic hypersensitivity to latex or to any of the vaccine components, or history of a life-threatening reaction to the vaccine(s) used in the study or to a vaccine containing any of the same substances 10) Verbal report of thrombocytopenia, as reported by the subject or the subject's parent / LAR, contraindicating intramuscular (IM) vaccination in the Investigator's opinion

	11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination in the Investigator's opinion 12) Personal history of Guillain-Barré syndrome 13) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within 10 years of the proposed study vaccination 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) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives. 18) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination, febrile illness (temperature ≥ 38.0°C), persistent diarrhea, vomiting. A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided 19) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 20) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
Statistical Methods:	All immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set (FAS) by randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS). ***Primary Objective*** *Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of the percentages of subjects who achieve ≥ 1:8 in hSBA titers in adolescents and children aged 2 to 17 years in India and RSA combined ([Gr 5 and Gr 7] versus [Gr 6 and Gr 8]).* Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the percentages of subjects who achieve ≥ 1:8 in hSBA titers for meningococcal serogroups A, C, Y, and W in the combined group (Gr 5 + Gr 7) are non-inferior to the corresponding percentages in the combined group (Gr 6 + Gr 8) Null hypothesis (H0): p(G5 + G7) - p(G6 + G8) ≤ -10% Alternative hypothesis (H1): p(G5 + G7) - p(G6 + G8) > -10% where p(G5 + G7) and p(G6 + G8) are the percentages of subjects who achieve ≥ 1:8 in hSBA titers in the combined group (Gr5 + Gr7) and the combined groups (Gr6 + Gr8), respectively.

	Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected. For the 4 non-inferiority hypotheses, the CI of the difference in proportions will be computed using the Wilson score method without continuity correction. The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.
	Secondary Objectives: *Immunogenicity* Secondary Objectives 1 and 2: Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in adults aged 18 to 55 years (Gr1 versus Gr2) or Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years (Gr3 versus Gr4) in India. Secondary Objectives 3, 4, and 5: Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in adolescents and children aged 2 to 17 years in India and RSA combined ([Gr5 + Gr7] versus [Gr6 + Gr8]), India only (Gr5 versus Gr6), and RSA only (Gr7 versus Gr8). In general, categorical variables in Cohort Ia, Ib (in India) and II (in India and RSA) will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. *Descriptive analyses on A, C, Y, and W serogroups on D0 and D30 (+14 days) using hSBA and rSBA (in a subset*) will be generated as follows:* Descriptive analyses of hSBA includes but will not be limited to: • Geometric mean titers (GMTs) and 95% CI • Titer distribution and reverse cumulative distribution curves (RCDCs) • Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with hSBA vaccine seroresponse† and 95% CI * rSBA data will be generated in a subset of subjects as follows: • Groups 1, 2, 3, and 4: 50 subjects each • Groups 5, 6, 7, and 8: 100 subjects each † hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as: • For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16 • For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

	Descriptive analyses of rSBA (in a subset) will include but not be limited to: • GMTs and 95% CI in a subset of age groups • Titer distribution and RCDCs • Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with rSBA vaccine seroresponse‡ and 95% CI in a subset of age groups ‡ rSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as: • a post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or • a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8 ***Observational Objectives*** *Immunogenicity* Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in children and adolescents aged 2 to 17 years and another set of descriptive statistics on the same children and adolescents by age groups 2 to 9 years and 10 to 17 years in India and RSA combined and separated by each country as well. In general, categorical variables for the full group aged 2 - 17 years and by age subgroups (2 to 9 years and 10 to 17 years) will be summarized and presented by frequency counts, percentages, and CIs in India and RSA combined ([Group 5 + Group 7] versus [Group 6 + Group 8]), India only (Gr5 versus Gr6), and RSA group only (Gr7 versus Gr8). 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. *Descriptive analyses on A, C, Y, and W serogroups on D0 and D30 (+14 days) using hSBA and rSBA (in a subset) will be generated as follows:* • Descriptive analyses of hSBA includes but will not be limited to: • GMTs and 95% CI • Titer distribution and RCDCs • Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with hSBA vaccine seroresponse† and 95% CI

	• Descriptive analyses of rSBA (in a subset) will include but not be limited to:
	  • GMTs and 95% CI in a subset of age groups
	  • Titer distribution and RCDCs
	  • Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
	  • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
	  • Percentage of subjects with rSBA vaccine seroresponse‡ and 95% CI in a subset of age groups
	
	Safety
	
	The SafAS is defined as those subjects who have received at least 1 dose of the study vaccine and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
	
	Safety analysis will include but not be limited to the following:
	
	• The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions occurring from D0 to D07 after vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken
	
	• Immediate unsolicited systemic AEs within 30 minutes and unsolicited AEs occurring up to D30 after vaccination will be summarized
	
	• The number and percentage of subjects reporting any unsolicited non-serious AEs will be summarized by study group, intensity, time of onset period, duration, and by MedDRA preferred term and system organ class (SOC), as well as by relationship to the study vaccine
	
	• The number and percentage of subjects reporting at least one of any SAEs will be summarized by study group, seriousness criterion, outcome, and by MedDRA preferred term and SOC, as well as by relationship to the study vaccine
	
	• The number and percentage of subjects reporting at least one of any AESIs will be summarized throughout the study
	
	• Exact (Clopper-Pearson) 2-sided 95% CIs will be calculated for the percentages
	
	Calculation of Sample Size:
	
	Approximately 1332 subjects will be enrolled. An estimated 15% drop-out rate (only ages 2 - 17 years) from enrollment will result in approximately 1190 subjects in the per-protocol population available for immunogenicity analyses.

For the Primary Objective

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

Table S1:Power of the study based on the primary objective of non-inferiority in children and adolescents aged 2 to 17 years

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

Note: Evaluable subjects:

Combined group (Gr5 + Gr7) = 395 subjects
Combined group (Gr6 + Gr8) = 396 subjects

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

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

Table of Study Procedures 1:
Groups 1 and 2 - Adults 18 to 55 years of age;
Groups 3 and 4 - Adults >= 56 Years of age

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

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

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

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

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

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

*Contact can be a telephone call, visit, or Outpatient Department Visit (OPDV) for India.
†If all other conditions and inclusion / exclusion criteria are met, then absence of the results of HIV testing will not prevent the randomization and vaccination of the subject. For subjects who had HIV testing prior to the enrollment visit (V01), the Investigator may decide to repeat the test if necessary at V01. The HIV testing will be performed at the study center using local accepted diagnostic test for HIV.
‡Temperature needs to be measured and recorded in source documents.
§Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.
**Blood sample at V01 will be drawn before administration of vaccine.
††Subjects will receive 1 dose of MenACYW conjugate vaccine or Menactra®. Children and adolescents (Cohort II) will not be vaccinated until after the favorable review of the safety data from adults in Cohorts Ia and Ib in India only.
‡‡This contact is made 8 to 10 days after the vaccination at V01. If D08 (+2 days) falls on a weekend or holiday, the contact

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

List of Abbreviations

µg	microgram
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CDM	Clinical Data Management
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CTA	Clinical Trial Agreement
CTL	Clinical Team Leader
DNB	Diplomate of National Board
DSMB	Data Safety Monitoring Board
EDC	electronic data capture
ESDR	Early Safety Data Review
FAS	Full Analysis Set
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
Gr	Group
hSBA	serum bactericidal assay using human complement
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IMD	invasive meningococcal disease
IME	important medical event
IOM	Institute of Medicine
IRB	Institutional Review Board
IRT	interactive response technology
LAR	Legally acceptable representative

LCLS	last contact, last subject
LLOQ	lower limit of quantitation
LLT	lowest level term
MBBS	Bachelor of Medicine and Bachelor of Surgery
MCC	Medicines Control Council
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
OPDV	outpatient department visit
OPV	oral poliovirus vaccine
PPAS	Per-Protocol Analysis Set
PV	Pharmacovigilance
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	Safety Analysis Set
SMT	Safety Management Team
TMF	trial master file
ULOQ	upper limit of quantitation
WHO	World Health Organization

1 Introduction

1.1 Background

This study (MET55) will use step-wise enrollment to evaluate and/or describe the immunogenicity and describe the safety of MenACYW conjugate vaccine in adults, adolescents, and children. The study populations will be recruited as cohorts, and older populations (adults) will be recruited before initiating the study in children and adolescents younger than 17 years of age.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *N. meningitidis*, a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). At least 12 different meningococcal serogroups have been classified based on the immunochemistry of the capsular polysaccharides. Some strains are more likely than others to cause infection (1) (2) (3). Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (2) (3) (4). Serogroup B is responsible for endemic disease and some outbreaks, while serogroup C is responsible for large outbreaks (5). Serogroup A remains the main cause of epidemics in the world and is especially dominant in Africa and Asia. Serogroup W has been observed in Africa, as well as the United Kingdom, in residents who participated in the Hajj pilgrimage to the Kingdom of Saudi Arabia (4) (6) (7) and more recently in Chile (8), Turkey (9) (10), China (11) (12), Argentina (13), Brazil (14) (15), and other parts of the world. Serogroup X causes substantial meningococcal disease in parts of Africa, but rarely causes disease in other parts of the world (2) (16). Serogroup Y has not been associated with outbreaks, but the frequency with which it causes sporadic cases has gradually increased in the US and more recently in Canada and Europe (17) (18) (19). The Y serogroup is commonly associated with meningococcal pneumonia, particularly in older adults ≥ 65 years of age (20). Outbreaks of serogroup B meningococcal disease have also been reported on college campuses in the US during the last five-year period: a prolonged outbreak of serogroup B on a university campus in Ohio from 2008 – 2010 and 2 universities in New Jersey and California in 2013 (21) (22).

The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. Meningococcal disease occurs worldwide in both endemic and epidemic forms with seasonal variation. In Europe, the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 19 year old group. The highest incidence rate in Europe is caused by serogroup B, followed by C (23). The highest proportion of meningococcal cases was due to serogroup B in the population under 5 years of age. The highest proportion of serogroup C cases was observed in the population 25 to 44 years of age while the proportion of serogroup Y cases was highest in the population aged 65 years and above.

A recent literature review provided data on the epidemiology of meningococcal disease in India over the last 100 years. The majority of the data presented were from observational hospital-based reports and from 2 unpublished reports from the Indian National Institute of Communicable Disease (24). The relatively few reports identified suggest that the incidence of endemic

meningococcal disease in India is low, but occasional epidemics have been registered. The larger epidemics have affected cities in northern India and have been caused mostly by serogroup A meningococci (24). Only 1 study provided an adequate denominator to define the incidence of bacterial meningitis during endemic periods. The authors estimated that the annual incidences of probable bacterial meningitis and of culture-confirmed meningitis of any cause in children under 5 years of age were 37 per 100,000 population and 15.9 per 100,000 population, respectively (25).

In the last 10 years, the emergence and global importance of serogroups W and Y have been recognized (26) (27). In the Republic of South Africa (RSA), since 2003 serogroup W has replaced serogroup A, causing hyper-sporadic incidence rate of disease (28). Recent molecular epidemiological studies using whole genome sequencing analyses suggest serogroup W belonging to the sequence type (ST11) clonal complex strains was the major cause of meningococcal disease worldwide (29) (30).

Incidence rates in RSA vary by province, but are currently low overall (0.36 / 100,000 in 2014). The majority of disease is caused by MenW followed by MenB; 66-77% of disease is caused by MenA, C, W or Y. The last peak in incidence in 2006, was attributed to MenW and MenW. ST11 remains the most prevalent with infection rates highest in infants and young children (2). The average incidence in the population over the last decade in RSA is 1 per 100,000 individuals with a peak of 8 per 100,000 infants; approximately 17% of those with meningococcal disease have died with case fatality rates increasing with age. Meningococcal caseloads wax and wane over periods of 5 to 10 years. RSA is possibly on the verge of seeing an increase in meningococcal disease in the near future since its peak in 2006. Although the incidence of meningococcal disease is currently low in RSA, the consequence of acquiring the disease can be devastating with high morbidity and mortality despite adequate treatment (31).

The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, Y, and W in all age groups including children as young as 6 weeks of age, adolescents, and adults, including those 56 years of age and older. The medical value of this vaccine in the age group 56 years and older in India is significantly important considering that a vast majority of Haj pilgrims from India fall in this age group and need regular vaccination with meningococcal vaccines.

1.2 Background of the Investigational Product

1.2.1 Clinical

The MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 to < 40 years of age; and MET32, a Phase I/II study in toddlers.

The formulation has been evaluated in over 2000 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in completed studies MET39, MET44, MET50, MET54, and MET56. MenACYW conjugate vaccine is also being evaluated in ongoing Phase III studies: MET51 and MET57 in toddlers (12 to 23 months of age); MET35 in children (2 to 9 years of age); MET43 in adolescents and adults (10 to 55 years of age); and MET49 in older adults (≥ 56 years of age).

MenACYW conjugate vaccine was found to be well tolerated and no unanticipated or new significant safety concerns have been identified in the clinical studies completed to date. The relevant Phase II studies are discussed below.

1.2.1.1 Study MET39 (Phase II)

MET39 was a Phase II, randomized, open-label, multi-center study conducted in the US for which 580 healthy subjects from 2 to 15 months of age were enrolled. This study evaluated the optimal vaccination schedule in the infant/toddler population. Subjects in Group 1 through Group 4 received 1, 2, or 3 primary doses plus an additional dose of the MenACYW conjugate vaccine in the second year of life, concomitantly with routine pediatric vaccines at several different vaccination schedules. Subjects in Group 5 received 1 dose of the MenACYW conjugate vaccine concomitantly with routine pediatric vaccines. The routine pediatric vaccines given concomitantly with MenACYW conjugate vaccine at various schedules included PREVNAR® (pneumococcal conjugate vaccine) or PREVNAR 13® (pneumococcal 13-valent conjugate vaccine [PCV13]), Pentacel® (diphtheria, tetanus, pertussis [acellular, component]-poliovirus [inactivated]//*Haemophilus influenzae* type b [DTaP-IPV//Hib]), ROTARIX® (monovalent rotavirus vaccine [RV1]) or RotaTeq® (pentavalent rotavirus vaccine[RV5]), hepatitis B vaccine, M-M-R® II vaccine (measles, mumps, and rubella vaccine [MMR]), and VARIVAX® (varicella vaccine).

Immunogenicity

After the primary series consisting of 1, 2, or 3 doses of MenACYW conjugate vaccine, protective serum bactericidal assay using human complement (hSBA) threshold titers of ≥ 1:8 were attained by > 88% of subjects for serogroup C and by 62% to 74% for serogroup A. For serogroups Y and W, ≥ 90% achieved the threshold titer after 3 doses, 75% to 84% after 2 doses, but only 25% after a single dose administered at 6 months of age.

After an additional dose of MenACYW conjugate vaccine in the second year of life (12 or 15 months), between 91% and 100% of the subjects achieved the protective threshold regardless of the number of doses they received in the first year of life.

Safety

MenACYW conjugate vaccine was well tolerated in infants and toddlers regardless of the immunization schedule and the number of doses administered. Safety results were comparable to those seen in control group subjects regardless of the immunization schedule and the number of doses administered. The safety profile of the licensed vaccines given concomitantly with MenACYW conjugate vaccine was similar to that of the licensed vaccines given concomitantly without MenACYW conjugate vaccine.

No deaths occurred within 30 days. There were 2 subjects in Group 4 who died during the study, 1 as a result of hypoxic ischemic encephalopathy which started 96 days after the 6-month vaccination and 1 as a result of non-accidental head trauma 36 days after the 12-month vaccination. These events were considered by the Investigator as unrelated to study vaccine. There were 2 other subjects who discontinued the study due to a serious adverse event (SAE) and the receipt of intravenous immunoglobulin treatment: 1 subject in Group 2 with Kawasaki disease, 106 days after the 6-month vaccination; and 1 subject in Group 3 with middle lobe

pneumonia and Kawasaki disease, 50 and 52 days, respectively, after the 4-month vaccinations. One other subject in Group 4 was discontinued due to a non-serious adverse event (AE) (viral rash 1 day after the 6-month vaccinations). None of these AEs leading to discontinuation were considered by the Investigator as related to the vaccine. There were no vaccine- related SAEs during this study.

1.2.1.2 Study MET44 (Phase II)

MET44 was a Phase II, randomized, open-label (the laboratory technicians were blinded to group assignment), multi-center study conducted in the US. This study evaluated the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine when administered to adults 56 years of age and older. A total of 301 subjects aged 56 years and older on the day of enrollment were randomized to receive a single dose of MenACYW conjugate vaccine or Menomune® - A/C/Y/W-135 vaccine; each group was stratified according to age into 2 subsets (subjects 56 to 64 years of age and subjects ≥ 65 years of age).

Immunogenicity

The proportions of subjects with hSBA titers ≥ 1:8 obtained after MenACYW conjugate vaccine administration (Group 1) for serogroups A and C were comparable to, or for serogroups Y and W higher than, those obtained after Menomune - A/C/Y/W-135 vaccine administration (Group 2): 93.8% in Group 1 and 85.1% in Group 2 for serogroup A; 74.9% in Group 1 and 62.8% in Group 2 for serogroup C; 80.5% in Group 1 and 59.6% in Group 2 for serogroup Y; 79.5% in Group 1 and 60.6% in Group 2 for serogroup W.

Within each group of those who received MenACYW conjugate vaccine or Menomune - A/C/Y/W-135 vaccine, the proportions of subjects with hSBA titers ≥ 1:8 were comparable between the subset of subjects 56 to 64 years of age and the subset ≥ 65 years of age, for all serogroups.

The hSBA geometric mean titers (GMTs) after MenACYW conjugate vaccine administration for serogroups A and W were comparable to, or for serogroups C and Y higher than, those after Menomune - A/C/Y/W-135 vaccine administration. Responses with serum bactericidal assay using baby rabbit complement (rSBA) in general demonstrated the same trend as with hSBA.

Safety

Vaccination with MenACYW conjugate vaccine or Menomune - A/C/Y/W-135 vaccine among adults 56 years of age and older was found to be well tolerated with no safety concerns identified. There were no immediate unsolicited AEs/reactions reported in either group. There were no deaths, SAEs or AEs that led to study discontinuation reported during the study.

The safety profile of the vaccine when compared by subject age was generally comparable between both age groups, with no clinical impact in the differences observed. In general, no increase in reactogenicity was observed in the older vaccine recipients as compared to the younger cohort in this study.

1.2.1.3 Study MET50 (Phase II)

MET50 was a Phase II, open-label, randomized, parallel-group, controlled, multi-center study to evaluate the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine compared to that of the licensed vaccine MENVEO®, and when MenACYW conjugate vaccine was given with Tdap and HPV vaccines, in 1715 healthy adolescents 10 to 17 years of age in the US.

Immunogenicity

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

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

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

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

Safety

Overall, vaccination with MenACYW conjugate vaccine among adolescents was found to be safe with no safety concerns identified when given alone or concomitantly with Tdap and HPV vaccines.

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

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

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

1.2.1.4 Study MET54 (Phase II)

MET54 was a Phase II, randomized, open-label, active-controlled, multi-center study conducted in Europe (Finland). This study evaluated the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine when given alone in healthy, meningococcal vaccine naïve toddlers compared to that of the licensed vaccine Nimenrix®. A total of 188 meningococcal

vaccine naïve subjects aged 12 to 23 months on the day of enrollment were randomized to 1 of 2 groups. Group 1 received a single dose of MenACYW conjugate vaccine and Group 2 received a single dose of Nimenrix®.

Immunogenicity

Antibody responses to the antigens (serogroups A, C, Y, and W) were evaluated by serum bactericidal assay using baby rabbit complement (rSBA) and human complement (hSBA). MenACYW conjugate vaccine immune responses evaluated by rSBA and hSBA were generally comparable to Nimenrix® immune responses with some variation by serogroup.

hSBA

Most subjects in both groups had hSBA titers ≥ 1:8 at D30: the percentages after MenACYW conjugate vaccine for serogroups A, Y, and W (ranging from 97.8% [89/91] to 98.9% [90/91]) were comparable to those after Nimenrix® (ranging from 91.9% [79/86] to 100.0% [86/86]). The percentage of subjects with hSBA titers ≥ 1:8 for serogroup C was higher after MenACYW conjugate vaccine (100.0% [91/91]) than after Nimenrix® (89.5% [77/86]). At D30, most subjects in both groups demonstrated an hSBA vaccine seroresponse. The percentage of subjects with an hSBA vaccine seroresponse for serogroups A, Y, and W was comparable in both groups (ranging from 96.7% [87/90] to 98.9% [90/91] after MenACYW conjugate vaccine and from 91.9% [79/86] to 98.8% [85/86] after Nimenrix®). The percentage of subjects with an hSBA vaccine seroresponse for serogroup C was higher after MenACYW conjugate vaccine (100.0% [91/91]) than after Nimenrix® (86.0% [74/86]).

rSBA

Most subjects had rSBA titers ≥ 1:128 at D30. The percentages after MenACYW conjugate vaccine were similar (100.0% [91/91] for serogroups A, Y, and W) or numerically higher (100.0% [91/91] for serogroup C) compared to Nimenrix® (100.0% [86/86] for serogroups A, Y, and W and 94.2% [81/86] for serogroup C). At D30, most subjects in both groups demonstrated an rSBA vaccine seroresponse as defined in the Statistical Analysis Plan (SAP) and as defined in the protocol. The percentage of subjects with any rSBA vaccine seroresponse by either definition for serogroup A was numerically lower after MenACYW conjugate vaccine (91.2% [83/91]) than Nimenrix® (98.8% [85/86]) and the percentages of subjects with any rSBA vaccine seroresponse by either definition were similar or comparable between the 2 groups for serogroups C, Y, and W (all > 96%).

Safety

Overall, vaccination with MenACYW conjugate vaccine among toddlers aged 12 to 23 months was found to be safe with no safety concerns identified. The MenACYW conjugate vaccine was well tolerated with no immediate AEs or adverse reactions (ARs), no discontinuations due to an SAE or other AE, and no related SAEs.

The safety profile of MenACYW conjugate vaccine was comparable to that of the licensed vaccine Nimenrix®.

No new clinically important safety findings were identified with administration of the MenACYW conjugate vaccine. The MenACYW conjugate vaccine was well tolerated and immunogenic. Single dose of the MenACYW conjugate vaccine demonstrated excellent potential

to be an alternative vaccine option for toddlers, receiving meningococcal vaccination for the first time.

1.2.1.5 Study MET56 (Phase III)

MET56 was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to compare the immunogenicity and describe the safety of a booster dose of MenACYW conjugate vaccine to a licensed vaccine in quadrivalent meningococcal conjugate vaccine-primed adolescents (≥ 15 to < 18 years) and adults (≥ 18 years) in the US. Approximately 800 healthy adolescents and adults who had received 1 dose of quadrivalent meningococcal conjugate vaccine 4 to 10 years previously were randomized in a 1:1 ratio to 1 of 2 groups: Group 1 MenACYW conjugate vaccine or Group 2 Menactra®.

Immunogenicity

MenACYW conjugate vaccine immune responses evaluated by hSBA and rSBA were generally comparable to Menactra® immune responses when given as a booster dose.

At D30, MenACYW conjugate vaccine was non-inferior to Menactra® for all 4 serogroups as measured by hSBA vaccine seroresponse.

At D06, the differences of the percentages of subjects achieving hSBA vaccine seroresponse between the MenACYW conjugate vaccine group and the Menactra® group were > 0 for serogroups A, Y, and W (6.6%, 7.0%, and 10.7%, respectively) and were < 0 for serogroup C (-3.5%), with overlapping 95% CIs.

At D30, the Group 1 / Group 2 hSBA GMT ratio ranged from 1.68 to 4.37 for all serogroups. At D30, meningococcal rSBA GMTs for all serogroups were higher after MenACYW conjugate vaccine than after Menactra® for all serogroups. The percentages of subjects with an rSBA vaccine seroresponse after vaccination with MenACYW conjugate vaccine were numerically higher than or comparable to the percentages after Menactra®.

MenACYW conjugate vaccine was comparable to Menactra® when immune response data was analyzed by age, time since first meningococcal vaccination, and quadrivalent meningococcal conjugate vaccine used for priming.

Safety

Overall, vaccination with a booster dose of MenACYW conjugate vaccine in quadrivalent meningococcal conjugate vaccine-primed adolescents and adults aged at least 15 years was found to be safe, with no safety concerns identified.

The safety profile of MenACYW conjugate vaccine was comparable to that of the licensed vaccine, Menactra®.

No new clinically important findings were identified with administration of a booster dose of MenACYW conjugate 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, and no safety issues have been detected to date. In all, the data support further evaluation of the MenACYW conjugate vaccine in humans.

Subjects who receive Menactra® or Quadri Meningo™ (or any licensed meningococcal vaccine) will likely be protected against meningococcal disease caused by *N. meningitidis* serogroups A, C, Y, and W.

As with any vaccine, MenACYW conjugate vaccine, Menactra®, or Quadri Meningo™ (or any licensed meningococcal vaccine) may not protect 100% of individuals against the diseases they are designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine, Menactra®, and Quadri Meningo™ (or any licensed meningococcal vaccine) may cause injection site reactions such as pain, swelling, and erythema, or certain systemic events such as fever, headache, malaise, and myalgia when administered to children, adolescents, or adults. Other common reactions following the administration of Menactra® in children 2 to 10 years of age also include induration at the injection site, irritability, diarrhea, and drowsiness. Common reactions following the administration of Menactra® in adolescents and adults 11 to 55 years of age also include induration at the injection site, fatigue, arthralgia, diarrhea, and loss of appetite. There may be a rare possibility of an allergic reaction, which could be severe. There may also be a risk of febrile convulsion in some children who experience high fever. There may be other risks for MenACYW conjugate vaccine, Menactra®, or Quadri Meningo™ (or any licensed meningococcal vaccine) that are not yet known.

The following additional adverse events (AEs) have been very rarely reported during post-approval use of Menactra®: Guillain-Barré syndrome (GBS), transverse myelitis, acute disseminated encephalomyelitis, vasovagal syncope, facial palsy, dizziness, paraesthesia, convulsion, lymphadenopathy, extensive limb swelling, 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® exposure.

GBS has been reported mostly in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of Menactra® (32). A retrospective cohort study carried out in the US using healthcare claims data found no evidence of increased GBS risk associated with the use of that vaccine. The study was able to exclude all but relatively small incremental risks (33).

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 (34). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (35). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (36).

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

In a previous study with MenACYW conjugate vaccine (MET32), 1 SAE of reactive arthritis reported in a toddler was considered by the Investigator to be related to the investigational vaccine. The subject developed right knee inflammation the day after receiving MenACYW conjugate vaccine, given by IM injection in the right deltoid. The subject recovered after treatment with ibuprofen and antibiotics. Results of the reactive arthritis investigations performed as part of the 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 completed studies.

The risk of vasovagal syncope exists after any vaccination in the adolescent age group. A few cases of immediate vasovagal-like response or syncope have been observed in adolescent subjects who had received MenACYW conjugate vaccine. Syncope has been reported following vaccination with Menactra®. Procedures should be in place to prevent falling injury and manage syncopal reactions.

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

The potential risk listed here are not exhaustive. Refer to the Investigator's Brochure of the investigational vaccine, the package insert for Quadri Meningo™ (37), and the package insert for Menactra® (38) for additional information regarding potential risks. In case using any other locally available licensed meningococcal vaccine, refer to its package insert for details.

1.4 Rationale for the Study

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

The MenACYW conjugate vaccine is designed to cover broader age groups than those covered by Menomune® -A/C/Y/W-135 and Menactra®. Menactra® has been very successful since its

licensure in 2005; however, it is not licensed in Europe and is not indicated in persons 8 months of age or younger or 56 years of age and older. While Menomune® -A/C/Y/W-135 and Menactra® are currently licensed in different parts of the world, the MenACYW conjugate vaccine is being developed by Sanofi Pasteur to ultimately replace Menomune® -A/C/Y/W-135 and Menactra® in the global market as a quadrivalent meningococcal conjugate vaccine indicated in infants/toddlers, children, adolescents, adults, and older adults ≥ 56 years of age. Meningococcal polysaccharide vaccines have 2 important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) polysaccharides alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of polysaccharide vaccines in infants and children has been shown to be improved by conjugating the polysaccharides to protein carriers. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of polysaccharide-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II studies including those with the final formulation (MET39 and MET44) and the recent Phase III studies showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above studies using the final formulation or in the earlier studies.

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

2 Study Objectives

2.1 Primary Objective

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

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

2.2 Secondary Objectives

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

3) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India and RSA
4) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India
5) To describe the antibody titers to the meningococcal serogroups A, C, Y, and W before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in RSA

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

2.3 Observational Objectives

Immunogenicity

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

Safety

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

The endpoint for the observational objective is presented in Section 9.3.1.1 and the endpoints for the observational safety objectives are presented in Section 9.3.2.2.

3 Investigators and Study Organization

This study will be conducted in approximately 12 sites in India and 7 sites in RSA. Details of the study centers and the Investigators at each center are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal Safety Management Team (SMT) and an independent Data Safety Monitoring Board (DSMB) will be utilized for this study. The DSMB committee will assess the progress of the clinical study and the safety data, and recommend to Sanofi Pasteur whether to continue, modify, or stop the study. The DSMB will be responsible for the evaluation of the safety of MenACYW conjugate vaccine and for making recommendations to the Sponsor on a medical and ethical basis. A formal DSMB review is proposed after capturing 7 days of safety information from a subset

(100 subjects across both cohorts) of subjects of the Adult Cohorts Ia and Ib before the enrollment of the children and adolescents in Cohort II for India only. A DSMB charter will be developed before study start.

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

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 Forms (ICFs), and the Assent Form, subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

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

The Investigator or Sponsor will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All SAEs occurring during the study will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

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

5.1.2 Justification of the Study Design

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

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

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

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

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

A DSMB will be used in this study. The DSMB will be involved in reviewing any life-threatening or fatal SAE cases considered as being related to vaccine throughout the study. Additionally, the study will be monitored by the DSMB, as they will be the only group with access to the unblinded data for the Early Safety Data Review (ESDR) that will take place prior to enrolling Cohort II in India. The DSMB will review the unblinded data and advise to either continue the study as planned or to stop the study. The procedures governing the function of the DSMB are outlined in the DSMB charter.

5.1.3 Study Plan

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

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

- Group 1 (MenACYW conjugate vaccine)
- Group 2 (Menactra®)

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

- Group 3 (MenACYW conjugate vaccine)
- Group 4 (Quadri Meningo™ or any locally available licensed meningococcal vaccine)

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

- Group 5 (MenACYW conjugate vaccine)
- Group 6 (Menactra®)

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

- Group 7 (MenACYW conjugate vaccine)
- Group 8: (Menactra®)

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

As an expectation of the regulatory agencies in India, it is proposed that this study will only use a step-wise approach for enrollment in India. Enrollment of Cohorts Ia (adults 18 to 55 years of age) and Ib (adults 56 years of age and older) will take place simultaneously. Enrollment of Cohort II will be initiated once the safety data collected from Day (D) 0 to D07 post-vaccination in a subset of first 100 subjects in adult Cohorts Ia and Ib (approximately first 10 subjects from each of the 12 sites across both cohorts) have been reviewed. This ESDR to assess whether proceeding to the younger age cohort (children and adolescents) in India is appropriate, will first be done by the Sponsor's SMT and subsequently by an independent DSMB that will be established for independent safety oversight of this study. RSA will not use a step-wise approach to enrollment and will enroll children and adolescents independent of India's ESDR design.

The safety of the investigational product will also be continuously monitored by the Sponsor throughout the study. Periodic safety data review will be performed by the Sponsor's SMT. For all safety reviews, blinded safety data will be provided to the Sponsor's SMT. A formal additional DSMB review is also proposed following completion of the study.

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

Safety data will be collected as follows: Immediate unsolicited systemic AEs will be collected within 30 minutes after vaccination. Solicited AE information will be collected from D0 to D07 after vaccination; unsolicited AE information will be collected from D0 to Visit (V) 02 after

vaccination, and SAE information (including AEs of special interest [AESIs]) will be collected throughout the study.

5.1.4 Visit Procedures

5.1.4.1 Cohort Ia and Ib (Groups 1-4)

V01 (D0): Inclusion, Randomization, Blood Sample, and Vaccination

1) *For India*: Obtain the consent from each subject for Audio-Visual (A-V) recording of the informed consent process before explaining the study and its procedures
2) Give the subject information about the study, answer any questions, obtain written informed consent, and give him / her a signed copy
3) Check inclusion and exclusion criteria for eligibility (see Section 5.2.4 and Section 5.2.5, respectively)
4) Collect demographic data
5) Urine pregnancy test, if applicable
6) Obtain verbal medical history about the subject, including ongoing medications
7) Conduct a history-directed physical examination, including temperature (a physical examination conducted during the same day as part of routine clinical care may be used for this purpose)
8) Connect to the interactive response technology (IRT) system for vaccine group randomization (at least allocation of dose number and subject number)
9) Obtain the first blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (no more than 3 attempts), then V01 can be rescheduled to a later date at which point informed consent and inclusion/exclusion criteria must be re-validated[a]. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.
10) Administer the appropriate study vaccine to the subject in the deltoid region. The vaccine must be administered on the side opposite to that of the blood sampling according to the study group:
    - Group 1 and Group 3 = MenACYW conjugate vaccine
    - Group 2 = Menactra®
    - Group 4 = Quadri Meningo™ (or any locally available licensed meningococcal vaccine)

[a] If the rescheduled visit is performed within the following 5 days, a physical examination does not need to be repeated unless the health status of the subject has visibly changed; however, if the rescheduled visit is performed after 5 days, a reassessment of the health status of the subject will be conducted to ensure that the subject is still healthy and eligible for participation.

11) Observe the subject for 30 minutes, and record any AE in the source document
12) Give the subject a diary card, a thermometer, and a ruler, and go over the instructions for their use
13) Remind the subject to expect a telephone call 3 days after V01 and to bring back the diary card when he/she returns for V02 at a specified date and time or have the diary card ready when the study representative contacts the subject as a part of the home visit
14) Remind the subject to notify the site in case of an SAE
15) Complete the relevant case report form (CRF) pages for this visit

Contact (3 to 5 Days After V01)

Note: If D03 falls on a weekend or a holiday, the contact[a] 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 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 D0 to D7 pages of the diary card
   - Complete the remaining pages of the diary card, and bring them to V02
   - Notify the site in case of an SAE

V01-D8 (D8 [+2] days after V01) Home or Outpatient Department Visit (OPDV): Collection of Safety Information

1) Review the diary card with the subject, including any AEs, medications, or therapy that occurred since vaccination and collect the safety data for D0 to D7 post-vaccination
2) Confirm with the subject the date of the next visit, remind the subject to complete the diary card and to bring it to V02
3) Complete the relevant CRF pages for this visit

V02 (30 [+14] days after V01): Collection of Safety Information and Blood Sample

1) Collect and review the pages of the diary card 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 second blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples)
4) Complete the relevant CRF pages for this visit and the termination record of the CRF
5) If the subject does not return for V02, 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

[a] Contact can be a telephone call, visit, or OPDV (for India)

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 5.2.11.

5.1.4.2 Cohort II (Groups 5 - 8)

V01 (D0): Inclusion, Randomization, Blood Sample, and Vaccination

1) *For India:* Obtain the consent from subject's parent(s) / LAR for A-V recording of the informed consent process before explaining the study and its procedures
2) *For RSA (Groups 7 and 8) only:* Obtain the consent from each subject, subject's parent(s) / LAR for HIV testing. If all other conditions and inclusion / exclusion criteria are met, then absence of the results of HIV testing will not prevent the randomization and vaccination of the subject. For subjects who had HIV testing prior to the enrollment visit (V01), the Investigator may decide to repeat the test if necessary at V01.
3) Give the subject's parent / LAR information about the study, answer any questions, obtain written informed consent and assent (for subjects 12 to 17 years of age), and give the subject's parent / LAR a signed copy of the ICF and a signed copy of the Assent Form (as applicable)
4) Check inclusion and exclusion criteria for eligibility (see Section 5.2.4 and Section 5.2.5, respectively)
5) Collect demographic data
6) Urine pregnancy test, if applicable
7) Obtain verbal medical history about the subject, including ongoing medications
8) Conduct a history-directed physical examination, including temperature (a physical examination conducted during the same day as part of routine clinical care may be used for this purpose)
9) Connect to the IRT system for vaccine group randomization (at least allocation of dose number and subject number)
10) Obtain the first blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (no more than 3 attempts), then Visit 1 can be rescheduled to a later date at which point informed consent and inclusion/exclusion criteria must be re-validated[a]. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.

[a] If the rescheduled visit is performed within the following 5 days, a physical examination does not need to be repeated unless the health status of the subject has visibly changed; however, if the rescheduled visit is performed after 5 days, a reassessment of the health status of the subject will be conducted to ensure that the subject is still healthy and eligible for participation.

11) *For RSA (Groups 7 and 8) only*: perform HIV test if subject gives consent. The HIV testing will be performed at the study center using local accepted diagnostic test for HIV.
12) Administer the appropriate study vaccine to the subject in the deltoid region[a]. The vaccine must be administered on the side opposite to that of the blood sampling according to the study group:
    - Group 5 and Group 7 = MenACYW conjugate vaccine
    - Group 6 and Group 8= Menactra®
13) Observe the subject for 30 minutes and record any AE in the source document
14) Give the subject's parent / LAR a diary card, a thermometer, and a ruler, and go over the instructions for their use
15) Remind the subject's parent / LAR to expect to be contacted 8 days after V01 and to bring back the diary card when they return for V02 at a specified date and time
16) Remind the subject's parent / LAR to notify the site in case of an SAE
17) Complete the relevant CRF pages for this visit

Contact (8 to 10 Days After V01)

Note: If D8 falls on a weekend or a holiday, the contact[b] may be made on the following business day. If the subject's parent / LAR 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 contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Remind the subject's parent / LAR to do the following:
    - Complete the diary card and bring it to V02
    - Notify the site in case of an SAE

V02 (30 [+14] days after V01): Collection of Safety Information and Blood Sample

1) Review the pages of the diary card with the subject's parent / LAR, 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 second blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples)
4) Complete the relevant CRF pages for this visit and the termination record of the CRF
5) If the subject's parent / LAR does not return for Visit 2, and the diary card is not received at the site, site personnel will contact the subject's parent / LAR by telephone. During the

[a] In case of malnourished subject (Z score = -2), the injection site can be the thigh instead of the deltoid region. This should be based upon Investigator judgement.

[b] Contact can be a telephone call, visit, or OPDV (for India).

telephone call, the subject's parent / LAR 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's parent / LAR with 3 attempts, the study personnel will follow instructions given in Section 5.2.11.

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

A 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 - First visit, first subject (FVFS) to last contact, last subject (LCLS): 15 October 2019 to 12 January 2021.

Planned inclusion period - FVFS to first visit, last subject (FVLS): 15 October 2019 to 12 December 2020 (this is for both cohorts FVFS of Cohort I to FVLS of Cohort II).

Planned vaccination period: 15 October 2019 to 12 December 2020.

Planned end of study: 09 February 2022.

Planned date of final clinical study report: 20 October 2021.

5.1.6 Early Safety Data Review

The safety of the investigational product will be continuously monitored by the Sponsor. In India, ESDR will be performed, the goal of which is to allow for a cautious, step-wise approach to vaccine administration. An initial safety review for this study is planned when a subset (100 subjects across both cohorts) of subjects in Cohorts Ia and Ib have been vaccinated and have provided safety data for D0 to D07 post-vaccination, using the data collection methods described in Section 5.1.3. The safety data collected will be entered into the case report books (CRBs), and will be summarized and reviewed by the Sponsor, initially in a blinded manner. It is understood that this review is based on preliminary data that have not been subject to validation and database lock.

The following safety parameters will be assessed as part of the early safety review:

- Immediate reactions
- Solicited injection site and systemic reactions
- Unsolicited AEs reported as related by the Investigator

- SAEs (including AESIs)

The data will be examined for the following alert thresholds defined for this study:

- Any deaths, regardless of causality
- Any vaccine-related SAEs
- Grade 3 fever reported in more than 5% of subjects

If any of the above criteria are met at the time of the ESDR, a decision will be made as to whether enrollment in the study will be allowed to resume. While safety for the specific cohort is reviewed, and until "go" decision is obtained by the internal SMT and DSMB, enrollment in the next cohort will not proceed. In addition, the option of partial or full unblinding is available to the Sponsor through the appointment of an independent statistician, if required, for a further in-depth review of the data.

Apart from the early safety review, the study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in India and RSA where the study is taking place.

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

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

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

In addition, a subject who visits the study site for a routine visit or a parent who brings a child to the study site for a routine visit may be invited to enroll in the study, if eligible. Subjects may also be recruited from the general population.

For India:

If a potential subject or subject's parent(s) / LAR is willing to participate in the study, first his/her consent for A-V recording of the study consent process will be obtained before explaining the study and its procedures with a signature in the A-V consent form. This explanation of the study and its procedures will be recorded through the A-V process. This is needed to ensure compliance with the regulations governing the consent process in India.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject and / or the parent / LAR 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 and / or LAR must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

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

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

If new information becomes available that may be relevant to the subject's or parent's / LAR'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.

For India, prior to enrollment, the Investigator or a designee will inform subjects or the parents / LARs of potentially eligible subjects about the study. They will explain to subjects or the parents / LARs that they may have to first sign an A-V consent form for A-V recording of the inform consent process as per local regulations.

In this study, each subject in India aged 7 to 11 years will give oral assent. In India and RSA; each subject aged 7 to 17 years will sign a separate Assent Form as required by local regulations. This form is to be used in addition to, not in place of, the ICF that is signed by the subject's parent / LAR. In RSA, the subjects and the parents / LAR will be asked to review and sign a form confirming their acceptance to get an HIV test done. Subjects or the parent(s) / LAR of each subject will be provided with an ICF describing the study design, the procedures for participation, and the discomfort related to the study. They will be given ample opportunity and time to enquire about the details of the study and their questions will be answered to their satisfaction. The Investigator, Sponsor, or staff of the Institution will not coerce or unduly influence them to participate or to continue to participate in the study. Once their doubts are clarified and they have made the decision about their participation or their child's participation in the study, they need to sign the ICF.

ICFs will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy will be kept by the subject or the subject's parent / LAR.

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) Age in the defined range on the day of inclusion

For Adults: Aged ≥ 18 years on the day of inclusion

For Children and Adolescents: Aged 2 to 17 years on the day of inclusion[a]

2) Z-score of ≥ -2 SD on the Weight-for-height table of the World Health Organization (WHO) Child Growth Standards

For Children : Children aged 2 to 5 years[b] must have a Z-score of ≥ -2 SD on the Weight-for-height table of the WHO Child Growth Standards

3) Informed consent obtained

For Adults: Informed Consent Form has been signed and dated by the subject and by an independent witness, if required by local regulations

For Children and Adolescents: Assent Form has been signed and dated by the subject (for subjects 7 to 17 years of age), and Informed Consent Form has been signed and dated by the parent(s) or legally acceptable representative and by an independent witness, if required by local regulations

4) Able to attend all scheduled visits and to comply with all study procedures

For Adults: Able to attend all scheduled visits and to comply with all study procedures

For Children and Adolescents: Subjects and parent / legally acceptable representative are 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 until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be pre-menarche, or post-menopausal for at least 1 year, or surgically sterile.
2) Participation at the time of study enrollment (or in the 4 weeks preceding the study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

[a] "2 to 17 years" means from the day of the 2nd birthday to the day before the 18th birthday.

[b] "2 to 5 years" means from the day of the 2nd birthday to the day before the 6th birthday.

3) Receipt of any vaccine in the 4 weeks (28 days) preceding the study vaccination or planned receipt of any vaccine in the 4 weeks following vaccination except for oral poliovirus vaccine (OPV) in India, received during national immunization days. In India, OPV may be received with a gap of at least 2 weeks before the study vaccine. This exception includes monovalent and bivalent OPV.
4) Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C,Y, or W; or meningococcal B serogroup containing vaccine)
5) Receipt of immune globulins, blood or blood-derived products in the past 3 months
6) Known or suspected congenital or acquired immunodeficiency[a]; 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)
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 traveling to countries with high endemic or epidemic disease)
9) Known systemic hypersensitivity to latex or to any of the vaccine components, or history of a life-threatening reaction to the vaccine(s) used in the study or to a vaccine containing any of the same substances[b]
10) Verbal report of thrombocytopenia, as reported by the subject or the subject's parent / legally acceptable representative, contraindicating intramuscular (IM) vaccination in the Investigator's opinion
11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination in the Investigator's opinion
12) Personal history of Guillain-Barré syndrome (GBS)
13) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within 10 years of the proposed study vaccination
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[c]

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[a] Subjects in RSA (ie, Groups 7 and 8) will be included regardless of the HIV test results.

[b] The components of the MenACYW conjugate vaccine are listed in Section 6.1.1 and in the Investigator's Brochure.

[c] 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.

17) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives
18) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination, febrile illness (temperature ≥ 38.0°C), persistent diarrhea, vomiting. A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
19) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
20) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

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 CRB. The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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

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

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

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

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable.

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

5.2.8 Contraindications for Subsequent Blood Draw

Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in

the sample collection falling outside of this 30 to 44 day timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.9 Conditions for Withdrawal

Subjects / parents / LARs will be informed that they have the right to withdraw /withdraw their child from the study at any time. A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns or significant noncompliance with the protocol (based on the Investigator's judgment), without the subject's permission (withdrawal)
- At the request of the subject / parent / LAR (drop-out)

The reason for a withdrawal or drop-out 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 (ie, documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the CRB and 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 or parent/LAR did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, noncompliance 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 a protocol deviation • The subject or the parent/LAR signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit
Withdrawal by Subject or Parent / LAR	To be used: • When the subject or parent / LAR indicated unwillingness to continue in the study • When the subject or parent / LAR made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.12 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, a protocol deviation, or loss of eligibility, including definitive contraindications.

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 / 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 1 dose of the study vaccine has been administered, the subject will not be discontinued from the study, but 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 (ie, details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be provided to the Sponsor within 1 month of delivery.

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

5.3 Safety Emergency Call

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

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

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

5.4 Modification of the Study and Protocol

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

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs / IRBs do not need to approve administrative changes; they only need to be notified when one is made.

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

5.5 Interruption of the Study

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

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

6 Vaccines Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product

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

Form:	Liquid solution
Dose:	0.5 milliliter (mL)
Route:	IM
Batch number:	To be determined

6.1.1.1 Composition

Each 0.5 mL dose of MenACYW conjugate vaccine 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]

6.1.1.2 Preparation and Administration

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

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

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

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

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

6.1.1.3 Dose Selection and Timing

Subjects in Groups 1, 3, 5, and 7 will receive 1 dose of MenACYW conjugate vaccine at V01.

6.1.2 Identity of Control Product 1

Menactra®: Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur Inc, Swiftwater, PA, USA)

Form: Sterile aqueous solution

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

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.1.2.1 Composition

Each 0.5 mL dose of Menactra® is formulated to contain the following ingredients:

Meningococcal (serogroup A) polysaccharide (monovalent conjugate).....4 µg
Meningococcal (serogroup C) polysaccharide (monovalent conjugate).....4 µg
Meningococcal (serogroup Y) polysaccharide (monovalent conjugate).....4 µg
Meningococcal (serogroup W-135) polysaccharide (monovalent conjugate).....4 µg

Diphtheria toxoid protein (carrier protein)..... 48 µg[a]
Sodium chloride (excipient) .....4.35 mg
Sodium phosphate (excipient) .....0.7 mg

6.1.2.2 Preparation and Administration

Menactra® is supplied in single-dose (0.5 mL) vials. One dose of Menactra® will be administered IM into the deltoid muscle of the arm.

The procedures for administering the control product are the same as those described for the study product in Section 6.1.1.2. See the Menactra® package insert (38) for details.

6.1.2.3 Dose Selection and Timing

Subjects in Groups 2, 6, and 8 will receive 1 dose of Menactra® at V01.

6.1.3 Identity of Control Product 2

Quadri Meningo™ (MenPS A,C,Y & W135): Meningococcal Polysaccharide Vaccine (Group A, C, Y & W135) (Bio-Med Pvt. Ltd., Uttar Pradesh, India) or any locally available licensed meningococcal vaccine indicated for the age will be used

Form: Lyophilisate for reconstitution with diluent to yield a solution for injection

Dose: 0.5 mL

Route: IM

Batch number: To be determined

[a] Diphtheria toxoid quantity is approximate and dependent on the conjugate polysaccharide to protein ratio

6.1.3.1 Composition

Each 0.5 mL dose is formulated to contain the following ingredients:

Purified polysaccharide of *Neisseria meningitidis* (*N. meningitidis*) Group A.....50 µg
Purified polysaccharide of *N. meningitidis* Group C.....50 µg
Purified polysaccharide of *N. meningitidis* Group Y .....50 µg
Purified polysaccharide of *N. meningitidis* Group W135 .....50 µg

Lactose (I.P.) (stabilizer).....5 mg
Thimerosal (I.P.) (preservative) .....0.05 mg

6.1.3.2 Preparation and Administration

Quadri Meningo™ is available in a single dose vial with syringe packing along with diluent (Isotonic Saline).

Reconstitute Quadri Meningo™ with diluent (0.5 mL for one dose) yielding clear solution. Inject 0.5 mL IM. See Quadri Meningo™ package insert (37) for details. In case using any other locally available licensed meningococcal vaccine, refer to its package insert for details.

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.3.3 Dose Selection and Timing

Subjects in Group 4 will receive 1 dose of Quadri Meningo™ (or any locally available licensed meningococcal vaccine) on D0.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

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

The investigational and control products will be supplied with investigational labeling and packaging. Each single dose of investigational or control product will be identified by a unique medication number on the carton label. In addition, the carton label will also have a detachable label for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

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

6.3.2.2 Product Storage

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

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C 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 (unblinded pharmacist / vaccination study staff) 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 (eg, because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT system to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

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

6.3.5 Recall of Products

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

6.4 Blinding and Code-breaking Procedures

This study is a modified double-blind study, which means that the subject's parent / LAR, the Investigator, and other study personnel remain unaware of the treatment assignments throughout the study. An unblinded vaccine administrator will administer the appropriate vaccine but will not be involved in safety data collection. The Sponsor and laboratory personnel performing the serology testing will also remain blinded to treatment assignments throughout the study until database lock.

The code may be broken in the event of an AE only when the identification of the vaccine received could influence the treatment of the subject. Code-breaking should be limited to the subject(s) experiencing the AE.

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking CRF is to be completed.

A request for the code to be broken may also be made:

- by the GPV Department through an internal system for reporting to Health authorities in the case of an SAE as described in International Council for Harmonisation (ICH) E2A. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (ie, the subject's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

The IEC / IRB must be notified of the code-breaking. All documentation pertaining to the event must be retained in the site's study records and in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

For India only:

In the case of ESDR, the Sponsor's SMT will first review the blinded and unclean data collected from D0 to D07 post-vaccination in a subset (100 subjects across both cohorts) of subjects in adult Cohorts Ia and Ib before enrollment proceeds. A formal DSMB review is also proposed for the D0 to D07 safety data before enrollment of children and adolescents in India proceeds.

6.5 Randomization and Allocation Procedures

For India, subjects will be assigned to 1 of 3 cohorts and randomized 1:1 to the groups within those cohorts.

On the day of enrollment, subjects in India (aged 18 to ≥ 56 years) who meet the inclusion / exclusion criteria and provide consent as described in Section 5.2.2 will be randomly assigned to Group 1 or Group 2 (Cohort 1a: subjects aged 18 to 55 years) or to Group 3 or Group 4 (Cohort 1b: subjects aged ≥ 56 years).

Cohort II will consist of adolescents and children aged 2 to 17 years from India and RSA. For India, subjects or subject's parent / LAR who sign the A-V recording form and provide consent as described in Section 5.2.2 will be randomly assigned to Group 5 or Group 6.

For RSA, subjects who sign the study Assent Form (for subjects aged 7 – 17 years) and whose parent / LAR signs the ICF will be randomly assigned to Group 7 or Group 8.

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

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 at least the subject number and vaccine dose number. The IRT system will also be used to allocate subjects in the rSBA subset as follows:

- Groups 1 – 4: 50 subjects each
- Groups 5 - 8: 100 subjects each

The full detailed procedures for randomization are described in the Operating Guidelines. If the subject is not eligible to participate in the study, then the 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 identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example, Subject 356 0001 00005 is the fifth subject enrolled in Center Number 1 in India (356 being the India country code). Subjects assigned to the rSBA subset will be identified with a 5-digit subject identifier that beings with "9". For example, Subject 356 0001 90005 is the fifth subject enrolled in Center Number 1 in India and is assigned to the rSBA subset.

Subject numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT system.

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications and Other Therapies

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

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

Collection Period in Source Documents

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

Categories of Reportable Medications and Reporting Period

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

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

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

- Category 1 medications will be reported in the CRB from the day of first vaccination to the end of the solicited and unsolicited follow-up period after each vaccination
- Category 2: Reportable medications with potential impact on the immune response of the study vaccines and used to define the Per-Protocol Analysis Set (PPAS). For example:

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

  - Influenza and other non-study vaccines: Influenza vaccine or OPV in the 2 weeks (14 days) preceding the study vaccination up to the last blood draw and any other vaccines (other than the study vaccine) in the 4 weeks preceding the study vaccination up to the last blood draw
  - Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
  - Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) within the past 3 months, anti-cancer chemotherapy, anti-proliferative drugs such as DNA synthesis inhibitors, or radiation therapy: used in the 6 months preceding the first study vaccination, and up to the last blood draw
    - Category 2 medications will be reported in the CRB according to the collection period detailed above up to the last blood draw
- Category 3: Systemic (oral or injectable) antibiotics, as they may interfere with bioassays used for antibody testing when taken before a blood draw.
  - Category 3 medications will be reported in the CRB for the period of 3 days (72 hours) before each blood draw

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

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

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

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

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

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

[a] Medication(s) prescribed for preventing AE occurrence (eg, paracetamol to reduce the risk of fever)

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at Visit 1 and 2. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At V01 and V02, 6 mL of blood from all subjects 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; will write the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; 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.

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

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

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

7.3 Sample Storage and Shipment

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

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

Class 6.2 specifications and the International Air Transport Association 602 packaging instructions.

Samples will be shipped to Global Clinical Immunology (GCI) at Sanofi Pasteur. The address is provided in the Operating Guidelines.

7.4 Future Use of Stored Biological Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 25 years after the end of the study. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

In addition, subjects / subjects' parents / LARs will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. 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, Assent Forms, CRBs, SAE reporting forms, Pregnancy Reporting forms, diary cards, 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 Endpoint and Assessment Method

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoint for the evaluation of immunogenicity is:

hSBA antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and at D30 (+14 days) after vaccination in adolescents and children aged 2 to 17 years in India and RSA ([Gr 5 + Gr 7] versus [Gr 6 + Gr 8])

9.1.1.2 Immunogenicity Assessment Methods

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

Antibodies to Meningococcal Antigens (HSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in hSBA. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with human complement are added to the serum dilutions and allowed to incubate. After this incubation period, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight at 37°C with 5% CO_2. Bacterial colonies present in the wells are then counted. The endpoint titer is determined by the reciprocal serum dilution yielding ≥ 50% killing as compared to the mean of the complement control wells. The lower limit of quantitation (LLOQ) of the hSBA assay is a titer of 1:4.

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

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

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

The secondary endpoints for the evaluation of immunogenicity are:

1) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and serum bactericidal assay using baby rabbit complement (rSBA) (in a subset)[a] before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in adults aged 18 to 55 years in India (Gr 1 versus Gr 2)
2) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[a] before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years in India (Gr 3 versus Gr 4)
3) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[a] before and at D30 (+ 14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India and RSA ([Gr 5 + Gr 7] versus [Gr 6 + Gr8])
4) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset)[a] before and at D30 (+ 14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in India (Gr 5 versus Gr 6)
5) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA (in a subset) [a] before and at D30 (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® in children and adolescents aged 2 to 17 years in RSA (Gr 7 versus Gr 8)

9.2.1.2 Immunogenicity Assessment Methods

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

The immunogenicity hSBA assessment method of the meningococcal serogroups A, C, Y, and W antibody titers for the secondary endpoints is the same as that presented in Section 9.1.1.2.

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

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

Antibodies to Meningococcal Antibodies (RSBA Method)

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

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

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

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

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 Immunogenicity Endpoint

The observational endpoints for the evaluation of immunogenicity are:

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

9.3.1.2 Immunogenicity Assessment Methods

The immunogenicity hSBA assessment method of the meningococcal serogroups A, C, Y, and W antibody titers for the observational endpoints is the same as that presented in Section 9.1.1.2.

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

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

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

The immunogenicity rSBA assessment method of the meningococcal serogroups A, C, Y, and W antibody titers for the observational endpoints is the same as that presented in Section 9.2.1.2.

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

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

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

9.3.2 Safety

9.3.2.1 Safety Definitions

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

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 (eg, asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

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

Adverse Reaction (AR):

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

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

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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" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (eg, injection site pain or headache occurring between D0 and D07 post-vaccination).

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

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

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D07 is a solicited reaction (ie, prelisted in the protocol and CRB), then a headache starting on D07 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

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

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

9.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination

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

9.3.2.3 Safety Assessment Methods

At V01 and V02, the Investigator or a delegate will ask the subject / parent / LAR about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

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 to Day 7 after Vaccination)

After vaccination, subjects, parents / LARs 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 (ie, D0 to D07) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions

- Action taken for each event (eg, medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

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

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, study staff will continue calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

Table 9.1, Table 9.2, and Table 9.3 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales. Note that Table 9.3 applies to all age groups in the study.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales for children (aged 2 to 9 years)

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
MedDRA PT	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

* For the subjective reaction of pain, parents / LARs will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.2: Solicited injection site reactions: terminology, definitions, and intensity scales for adolescents and adults (aged 10 to >= 56 years)

CRB term (MedDRA LLT)	Injection site pain	Injection site erythema	Injection site swelling
MedDRA PT	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subjects Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

* For the subjective reaction of pain, subjects / parents / LARs will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

Table 9.3: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA LLT)	**Fever**	**Headache**	**Malaise**	**Myalgia**
MedDRA PT)	Pyrexia	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subjects.	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 subjects.	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 subjects.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

* For all reactions but fever, subjects or parents / LARs will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important Notes for the Accurate Assessment of Temperature:

Subjects / parents / LARs are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is axillary. Pre-vaccination temperature is also systematically collected by the Investigator on the source document. Tympanic thermometers must not be used.

9.3.2.3.3 Unsolicited Adverse Events

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

Information on SAEs will be collected and assessed throughout the study, from the time of vaccination until Day 30 after vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports). In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE. See 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, Table 9.2, and Table 9.3).

[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.

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

- Grade 1: A type of AEs that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living
- Grade 2: A type of AEs that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject
- Grade 3: A type of AEs that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

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

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

- Action taken for each AE (eg, medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- Whether the AE was serious

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

- Whether the AE caused study discontinuation

9.3.2.3.4 Adverse Events of Special Interest

An AESI is defined as an event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. The following AEs will be captured as AESIs throughout the study:

- Generalized seizures (febrile and non-febrile) (39) (40)
- Kawasaki disease (41) (42) (43)
- GBS (44)
- Idiopathic thrombocytopenic purpura (ITP) (45) (46)

These events have been listed as AESIs based on the feedback received from the European Union regulators.

No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in the completed clinical studies. 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.

AEs likely to be related to the product, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

9.3.3 Efficacy

No clinical efficacy data will be obtained in the study.

10 Reporting of Serious Adverse Events

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

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the study or experiment must be reported within 24 hours from its occurrence to the chairman of the IEC, the Licensing Authority (DCGI), 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, DNB, or MBBS]) 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 CTL 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: [redacted]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted]
- By express mail, to the following address:

  Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global PharmacoVigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370

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

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

10.2 Follow-up Reporting by the Investigator

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

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

For India, the SAE follow-up report must be submitted within 14 calendar days of SAE occurrence to the chairman of the respective IEC, Licensing Authority (DCGI), head of the Institution where the study has been conducted, and the Sponsor's GPV department.

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

Any SAE that occurs after a subject has completed the study but that is likely to be related to the investigational product(s), 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 Pharmacovigilance (PV) 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 the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

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

10.5.1 Opinion Report by IEC to Health Authorities

For India:

After communication of the SAE to the IEC, the IEC should share with the DCGI the following within 30 calendar days:

1) The opinion report on the SAE and
2) Its recommendation on the financial compensation of the subject

The Investigator of the site should follow-up with the respective IEC/IRB whether it provided to the DCGI the required details or not. The Investigator should share the communication with the Sponsor.

For RSA:

AEs/ARs should be submitted to the Medicines Control Council (MCC), now SAHPRA (South African Health Products Regulatory Authority).

For unexpected SAEs/serious ARs that are not fatal or life-threatening,, not later than 15 calendar days after first knowledge of the Sponsor; for fatal-should be within 7 calendar days after first knowledge by applicant and the initial notification must be followed up or completed within an additional 8 calendar days. Any suggested change in nature, severity or frequency of expected AEs/ARs or when new risk factors are identified should be communicated to the MCC within 15 calendar days after first knowledge by Sponsor. Any information which may influence benefit-risk assessment or that which could change in the administration of the investigational product or in the overall conduct of a clinical study must be reported to the MCC within 3 calendar days of the first knowledge (47).

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study subjects 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, Table 9.2, and Table 9.3) as well as areas for free text to capture additional safety information or other relevant details. Subjects / parents or LARs will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects / parents / LARs on how to correctly use these tools.

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

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

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

trail will be initiated in the EDC system at the time of the first data entry to track all modifications and ensure database integrity.

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

11.2 Data Management

Management of SAE 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 PV Global Safety Expert and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

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

Management of Clinical and Laboratory Data

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

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

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

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 blind review of the data is anticipated through the data review process led by Data Management before database lock. The safety of the investigational product will be continuously monitored by the Sponsor. Periodic blinded safety data reviews will be performed by the Sponsor's SMT.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Clinical data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor.

A SAP will be written and peer reviewed before any analyses. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 Hypotheses

Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the percentages of subjects who achieve ≥ 1:8 in hSBA titers for meningococcal serogroups A, C, Y, and W in the combined group (Gr 5 + Gr 7) are non-inferior to the corresponding percentages in the combined group (Gr 6 + Gr8)

Null hypothesis (H0): $p(G5 + G7) - p(G6 + 8) \leq -10\%$

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

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

Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected.

For the 4 non-inferiority hypotheses, the CI of the difference in proportions will be computed using the Wilson score method without continuity correction (48). The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Hypotheses

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

12.1.2.2 Statistical Methods

Immunogenicity

Secondary Objectives 1 and 2:

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in adults aged 18 to 55 years (Gr1 versus Gr2) or Quadri Meningo™ (or any locally available licensed meningococcal vaccine) in adults aged ≥ 56 years (Gr3 versus Gr4) in India.

Secondary Objectives 3, 4, and 5:

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menactra® in adolescents and children aged 2 to 17 years in India and RSA combined ([Gr5 + Gr7] versus [Gr6 + Gr8]), India only (Gr5 versus Gr6), and RSA only (Gr7 versus Gr8).

In general, categorical variables in Cohorts Ia and Ib (in India) and II (in India and RSA) will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) (49) for percentages.

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

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

- GMTs and 95% CI
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse[b] and 95% CI

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

[b] hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:
- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16;
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

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

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

12.1.3 Statistical Methods for Observational Objectives

Immunogenicity

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

In general, categorical variables for the full group in Cohort II and by age groups (2 to 9 years and 10 to 17 years) will be summarized and presented by frequency counts, percentages, and CIs in India and RSA combined ([Gr 5 + Gr7]) versus [Gr 6 + Gr8]), India only (Gr 5 versus Gr6), and RSA only (Gr7 versus Gr8). The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) (49) for percentages.

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

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

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

[a] rSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:
- a post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or
- a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8.

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

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

Safety

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

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

- The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions occurring from D0 to D07 after vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken
- Immediate unsolicited systemic AEs within 30 minutes and unsolicited AEs occurring up to D30 after vaccination will be summarized
- The number and percentage of subjects reporting any unsolicited non-serious AEs will be summarized by study group, intensity, time of onset period, duration, and by MedDRA preferred term and system organ class (SOC), as well as by relationship to the study vaccine
- The number and percentage of subjects reporting at least one of any SAEs will be summarized by study group, seriousness criterion, outcome, and by MedDRA preferred term and SOC, as well as by relationship to the study vaccine
- The number and percentage of subjects reporting at least one of any AESIs will be summarized throughout the study
- Exact (Clopper-Pearson) (49) 2-sided 95% CIs will be calculated for the percentages

For exploratory purpose, main safety and immunogenicity parameters may be presented according to baseline HIV status in Groups 7 and 8. Further details will be included in the SAP.

12.2 Analysis Sets

Three analysis sets will be used: the Full Analysis Set (FAS), the PPAS, and the SafAS.

12.2.1 Full Analysis Set

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

12.2.2 Safety Analysis Set

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

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

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

12.2.3 Per-Protocol Analysis Set

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

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

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

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

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

12.2.4 Populations Used in Analyses

The primary immunogenicity analyses will be performed on the PPAS analysis set and will be confirmed on the FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

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

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

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

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

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

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

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

12.4 Interim / Preliminary Analysis

No interim analyses are planned.

12.5 Determination of Sample Size and Power Calculation

Calculation of Sample Size:

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

For the Primary Objective

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

Table 12.1: Power of the study based on the primary objective of non-inferiority in children and adolescents aged 2 to 17 years

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

Note: Evaluable subjects:
Combined group (Gr5 + Gr7) = 396 subjects
Combined group (Gr 6 + Gr8) = 396 subjects

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

* Estimated seroresponses are based on the results of a study (50) conducted in India in subjects aged 2 to 75 years. The estimates were the average of overall rates of 2 age groups (2 to 10 years and 11 to 18 years). Borrow et al. reported that incidence rates vary in RSA by province but are currently low overall (0.36/100 000 in 2014) with the majority of disease caused by MenW, followed by MenB. Approximately 66-77% of disease is caused by MenA, C, Y, or W. Due to any lack of published data from RSA it is assumed that the response in subjects aged 2-17 years will be similar between India and RSA. Additionally, any variability should balance itself out due to the wider age range.

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

[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.

applicable laws and regulations, including the GDPR (Global Data Protection Regulation). Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subjects' ethnicity will be collected in this study with other personal characteristics because these data may affect immune response to the vaccine.

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 that would make the subject identifiable will not be transferred.

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

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

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the study (ie, 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 the product management and sample-handling procedures.

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

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (eg, protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

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

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

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical Quality Assessment department 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 must keep all study documents after the completion or discontinuation of the study, whatever the nature of the investigational center (private practice, hospital, or Institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, study documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). The PI and the Institution 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 longest of the 2 following periods ("Retention Period"):

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

If during the Retention Period, the Institution is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), the Institution 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 PI and / or the Institution are responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

In addition, study documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the study documents.

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 CTA 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.

Payment for medical management and compensation will be provided as per local regulations.

13.6 Stipends and Compensation 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.

For India only:

Compensation in case of injury or death during clinical study: As per Rule 122-DAB of ***G.S.R*** 53(E) released by Ministry of Health and Family Welfare (Department of Health) Government of India, Notification Dated 31 December 2016.

- In case of an injury occurring to the subject during the clinical study, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical study, whichever is earlier
- In case the injury occurring to the study subject is related to the clinical study, such subject shall also be entitled for financial compensation as per order of the Licensing Authority defined under clause (b) of Rule 21[a], and the financial compensation will be over and above any expenses incurred on the medical management of the subject
    - In case there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages of the subject

[a] Rule 21 clause b states: "licensing authority" means the authority appointed by the Central Government to perform the duties of the licensing authority under these Rules and includes any person to whom the powers of a licensing authority may be delegated under Rule 22. Rule 22 states: The licensing authority may, with the approval of the Central Government, by an order in writing delegate the power to sign licenses and Registration Certificate and such other powers as may be specified in the order to any other person under his control.

- In the case of clinical study-related death of the subject, his / her nominee(s) would be entitled for financial compensation, as per the order of the Licensing Authority defined under clause (b) of Rule 21 and the financial compensation will be over and above any expenses incurred on the medical management of such subject
- The expenses on medical management and financial compensation in the case of clinical study injury or death of the study subject shall be borne by the Sponsor of the clinical study.
- Any injury or death of the subject occurring in clinical study due to following reasons shall be considered as clinical study-related injury or death and the subject or his / her nominee(s), as the case may be, are entitled for financial compensation for such injury or death:
  - Adverse effect of investigational product(s)
  - Violation of the approved protocol, scientific misconduct, or negligence by the Sponsor or his representative or the Investigator
  - Failure of investigational product to provide intended therapeutic effect where the standard care, though available, was not provided to the subject as per the clinical study protocol
  - Use of placebo in a placebo-controlled study where the standard care, though available, was not provided to the subject as per the clinical study protocol
  - Adverse effects due to the concomitant medication excluding standard care, necessitated as part of approved protocol
  - For injury to a child in-utero because of the participation of parent in clinical study
  - Any clinical study procedures involved in the study
- The Sponsor, whether a pharmaceutical company or an Institution, shall give an undertaking along with the application for clinical study permission to the Licensing Authority defined in clause (b) of Rule 21, to provide compensation in the case of clinical study-related injury or death for which subjects are entitled to compensation
- In case the Sponsor fails to provide medical management for the injury to the subjects and / or financial compensation to the study subject for clinical study-related injury or financial compensation to the subject's nominee(s) in case of clinical study-related death of the subject, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing, stating the reasons thereof, suspend or cancel the clinical study and / or restrict Sponsor including his representative(s) to conduct any further clinical studies in the country or take any other action deemed fit under the rules

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.

14 Reference List

1 Harrison LH, Granoff DM, Pollard AJ. Meningococcal capsular group A, C, W, and Y conjugate vaccines. In: Plotkin SA, Orenstein WA, Offit PA, Edwards KM, editors. Vaccines. 7th ed. Philadelphia (PA): Elsevier;2018:619-43.

2 Borrow R, Alarcón P, Carlos J, et al. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines. 2017;16(4):313-28.

3 Harrison OB, Claus H, Jiang Y, et al. Description and nomenclature of Neisseria meningitidis capsule locus. Emerg Infect Dis. 2013;19(4):566-73.

4 Pollard AJ. Global epidemiology of meningococcal disease and vaccine efficacy. Pediatr Infect Dis J. 2004;23(12 Supp):S274-9.

5 Kvalsvig AJ, Unsworth DJ. The immunopathogenesis of meningococcal disease. J Clin Pathol. 2003;56(6):417-22.

6 Sidikou F, Djibo S, Taha MK, et al. Polymerase chain reaction assay and bacterial meningitis surveillance in remote areas, Niger. Emerg Infect Dis. 2003;9(11):1486-8.

7 World Health Organization. Meningococcal disease, serogroup W135 (update). WER. 2001;76(28):213-4.

8 Sáfadi MA, O'Ryan M, Valenzuela Bravo MT, et al. The current situation of meningococcal disease in Latin America and updated Global Meningococcal Initiative (GMI) recommendations. Vaccine. 2015;33(48):6529-36.

9 Ceyhan M, Yildirim I, Balmer P, et al. A prospective study of etiology of childhood acute bacterial meningitis, Turkey. Emerg Infect Dis. 2008;14(7):1089-96.

10 Kilic A, Urwin R, Li H, Saracli MA, Stratton CW, Tang YW. Clonal spread of serogroup W135 meningococcal disease in Turkey. J Clin Microbiol. 2006;44(1)222-4.

11 Shao Z, Zhou H, Gao Y, et al. Neisseria meningitidis serogroup W135, China. Emerg Infect Dis. 2010;16(2):348-9.

12 Zhou H, Liu W, Xu L, et al. Spread of Neisseria meningitidis serogroup W clone, China. Emerg Infect Dis. 2013;19(9):1496-9.

13 Efron AM, Sorhouet C, Salcedo C, Abad R, Regueira M, Vasquez JA. W135 invasive meningococcal strains spreading in South America: significant increase in incidence rate in Argentina. J Clin Microbiol. 2009;47(6):1979-80.

14 Weidlich L, Baethgen LF, Mayer LW, et al. High prevalence of Neisseria meningitidis hypervirulent lineages and emergence of W135:P1.5,2:ST-11 clone in southern Brazil. J Infect. 2008;57(4):324-31.

15 Barroso DE, Rebelo MC. Recognition of the epidemiological significance of Neisseria meningitidis capsular serogroup W135 in the Rio de Janeiro region, Brazil. Mem Inst Oswaldo Crus. 2007;102(6):773-5.

16 Boisier P, Nicholas P, Djibo S, et al. Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in 2006 in Niger. Clin Infect Dis. 2007;44(5):657-63.

17 Rosenstein NE, Perkins BA, Stephens DS, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis. 1999;180(6):1894-901.

18 Canadian Immunization Committee and Public Health Agency of Canada. Advice for consideration of quadrivalent (A, C, Y, W135) meningococcal conjugate vaccine, for use by provinces and territories. CCDR. 2010;36(S2):1-35.

19 Bröker M, Jacobsson S, Kuusi M, et al. Meningococcal serogroup Y emergence in Europe: update 2011. Hum Vaccin Immunother. 2012;8(12):1907-11.

20 Cohn AC, MacNeil JR, Harrison LH, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease. Clin Infect Dis. 2010;50(2):184-91.

21 National Foundation for Infectious Diseases. Addressing the challenges of serogroup B meningococcal disease outbreaks on campuses: A report by the National Foundation for Infectious Diseases. May 2014. Available from: http://www.nfid.org/meningococcal-b. Accessed 05 July 2017.

22 Centers for Disease Control and Prevention. Interim guidance for control of serogroup B meningococcal disease outbreaks in organizational settings. Available from: http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf. Accessed 05 July 2017.

23 European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe 2008/2009. Stockholm: ECDC; 2011. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/1107_SUR_IBD_2008-09.pdf. Accessed on 12 July 2017.

24 Sinclair D, Preziosi MP, John TJ, Greenwood B. The epidemiology of meningococcal disease in India. Trop Med Int Health. 2010;15(12):1421-35.

25 Minz S, Balraj V, Lalitha MK, et al. Incidence of Haemophilus influenzae type b meningitis in India. Indian J Med Res. 2008;128:57-64.

26 Mueller J, Borrow R, Gessner B. Meningococcal serogroup W135 in the African meningitis belt: epidemiology, immunity, and vaccines. Exp Rev Vacc. 2006;5(3):319-36.

27 Harrison LH, Shutt KA, Schmink SE, et al. Population structure and capsular switching of invasive Neisseria meningitidis isolates in the pre-meningococcal conjugate vaccine era-United States, 2000-2005. J Infect Dis. 2010;201:1208-24.

28 von Gottberg A, du PM, Cohen C, et al. Emergence of endemic serogroup W135 meningococcal disease associated with a high mortality rate in South Africa. Clin Infect Dis. 2008;46(3):377-86.

29 Abad R, López EL, Debbag R, Vázquez JA. Serogroup W meningococcal disease: global spread and current affect on the Southern Cone in Latin America. Epidemiol Infect. 2014;142(12):2461-70.

30 Mustapha MM, Marsh JW, Harrison LH. Global epidemiology of capsular group W meningococcal disease (1970-2015): Multifocal emergence and persistence of hypervirulent sequence type (ST)-11 clonal complex. Vaccine. 2016;34(13):1515-23.

31 Meiring S, Hussey G, Jeena P, Parker S and von Gottberg A. Recommendations for the use of meningococcal vaccines in South Africa. South Afr J Infect Dis 2017:32 (3):82-86.

32 Centers for Disease Control and Prevention. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine--United States, June 2005-September 2006. MMWR. 2006; 55(41):1120-4.

33 Velentgas P, Amato AA, Bohn RL, et al. Risk of Guillain-Barré syndrome after meningococcal conjugate vaccination. Pharmacoepidemiol Drug Saf. 2012;21(12):1350-8.

34 Institute of Medicine. Diphtheria toxoid, tetanus toxoid, and acellular pertussis-containing vaccines. In: Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press;2012:557-8. https://doi.org/10.17226/13164.

35 Institute of Medicine. Diphtheria and tetanus toxoids. In: Adverse events associated with childhood vaccines: evidence bearing on causality. Washington, DC. The National Academies Press; 1994:67-117. https://doi.org/10.17226/2138.

36 Centers for Disease Control and Prevention. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP):MMWR. 2011;60(2):1-60.

37 Quadri Meningo [package insert]. Bio-Med Pvt. Ltd., Uttar Pradesh, India. Available from: http://biomed.co.in/quadrimeningo.html. Accessed on 13 October 2017.

38 Menactra [package insert]. Sanofi Pasteur India Private Limited, Mumbai, India.

39 Bonhoeffer J, Menkes J, Gold MS, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004;22:557-62.

40 Marcy SM, Kohl KS, Dagan R, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004; 22(5-6):551-6.

41 Phuong LK, Bonetto C, Buttery J, et al and Brighton Collaboration Kawasaki Disease Working Group. Kawasaki disease and immunisation: standardised case definition & guidelines for data collection, analysis. Vaccine. 2016;34(15):6582-96.

42 Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics. 2004;114(6):1708-33.

43 Centers for Disease Control and Prevention. Kawasaki Syndrome Case Report 2003. Available from: http://www.cdc.gov/kawasaki/pdf/ks_case_report-fillable.pdf. Accessed 06 December 2017.

44 Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

45 Wise RP, Bonhoeffer J, Beeler J, et al. Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5717-24.

46 Chu YW, Korb J, Sakamoto M. Idiopathic thrombocytopenic purpura. Pediatr Rev. 2000;21(3):95-104.

47 National Institute of Allergy and Infectious Diseases. Clin Regs. Available at: https://clinregs.niaid.nih.gov/country/south-africa#safety_reporting. Accessed 21 June 2018.

48 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998;17:873-90.

49 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17:857-72.

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

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