NCT Number:NCT02955797

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Toddlers 12 to 23 Months of Age

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a single dose of MenACYW conjugate vaccine to a single dose of a licensed quadrivalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine (MenACWY-TT) in toddlers in the European Union who are either meningococcal vaccine naïve or received MenC vaccination during infancy.

Clinical Trial Protocol

Health Authority File Number:	EudraCT #: 2016-000749-30
WHO Universal Trial Number (UTN):	U1111-1161-2935
Trial Code:	MET51
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 as a single dose in toddlers 12 to 23 months old
Manufacturer:	Same as Sponsor
Coordinating Investigators:	To be determined
Sponsor's Responsible Medical Officer:	[redacted], Sanofi Pasteur Inc. Address: [redacted] Tel: Mobile: Fax:
Product Safety Officer:	[redacted], Sanofi Pasteur Inc. Tel: Fax:
Regional Clinical Trial Manager:	[redacted], Sanofi Pasteur SA Address: [redacted] Tel:
Version and Date of the Protocol:	Version 2.0 dated 20 July 2016

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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 Trial:	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Toddlers 12 to 23 Months of Age
Development Phase:	Phase III
Coordinating Investigators:	To be determined
Trial Centers:	This will be a multi-center, multi-national trial with approximately 32 to 40 trial centers in European countries. Approximately 35 trial centers in Spain, Hungary, Germany, and Finland will be included in the trial. Other countries may potentially be included if needed to meet enrollment goals. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	1Q 2017 – Q4 2017
Trial Design and Methodology:	This will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a single dose of MenACYW conjugate vaccine to a single dose of a licensed quadrivalent meningococcal polysaccharide groups A, C, W-135, and Y conjugate vaccine (MenACWY-TT, Nimenrix®) in toddlers (12 to 23 months of age) in the EU who are either meningococcal vaccine naïve or received monovalent MenC vaccination during infancy. Approximately 918 healthy toddlers aged 12 to 23 months will be enrolled and randomized as follows depending on the meningococcal background: **Meningococcal Vaccine-Naïve Subjects**: 612 subjects will be randomized in a 1:1 ratio to the following 2 groups: • Group 1: MenACYW conjugate vaccine (n=306) • Group 2: Nimenrix® (n=306) **MenC-Primed Subjects:** 306 subjects will be randomized in a 2:1 ratio to the following 2 groups: • Group 3: MenACYW conjugate vaccine (n=204) • Group 4: Nimenrix® (n=102) Enrollment of MenC-primed subjects will be stratified by the type of primed vaccine, MenC-TT (NeisVac-C®) or MenC-CRM (Menjugate®, Meningitec®), considering that at least 25% and a maximum of 50% of subjects will have been primed with MenC-CRM as described in Table S1:

<table>
<tr><td></td><td>
Table S1: MenC priming strategy
<table>
<tr><th>Priming</th><th>Group 3
MenACYW conjugate vaccine</th><th>Group 4
Nimenrix®</th></tr>
<tr><td>MenC-TT</td><td>102 - 152*</td><td>51 - 76*</td></tr>
<tr><td>MenC-CRM</td><td>52* - 102</td><td>26* - 51</td></tr>
<tr><td>Total</td><td>204</td><td>102</td></tr>
</table>
*Sample size corresponding to 25% of subjects primed with MenC-CRM
All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days post-vaccination. Solicited adverse event (AE) information will be collected for 7 days after vaccination, unsolicited AE information will be collected from Visit (V) 01 Day (D) 0 to V02 (D30 + 14 days), and serious adverse event (SAE) information, [redacted] will be collected throughout the trial.
</td></tr>
<tr><td>Early Safety Data Review:</td><td>This trial will not include an early review of safety data (i.e., no early safety review of preliminary safety data occurring at pre-determined milestones defined in the protocol with pause in enrollment). However, it 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/Institutional Review Boards (IECs/IRBs), or the governing regulatory authorities in the countries where the trial is taking place.
If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the subjects' parent/legally acceptable representative and should assure appropriate therapy and follow-up.</td></tr>
<tr><td>Primary Objectives:</td><td>1) To demonstrate the non-inferiority of the antibody response to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
2) To demonstrate the non-inferiority of the antibody response to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers</td></tr>
<tr><td>Primary Endpoints:</td><td>1) Antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
2) Antibody titers.≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers</td></tr>
</table>

Secondary Objectives:	1) To compare the antibody responses (geometric mean titers [GMTs]) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy 2) To compare the antibody responses (GMTs) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in meningococcal vaccine naïve toddlers 3) To compare the antibody responses (GMTs) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in toddlers who received monovalent MenC vaccination during infancy
Secondary Endpoints:	1) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy 2) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers 3) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccination during infancy

Observational Objectives:	***Immunogenicity***
	• To describe the antibody response to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after a dose of MenACYW conjugate vaccine or Nimenrix® in terms of serum bactericidal assay using baby rabbit complement (rSBA) titers ≥ 1:8 and ≥ 1:128 in toddlers in a subset of subjects per group:
	  ◦ Group 1 and Group 2: 100 subjects each
	  ◦ Group 3: 50 subjects in each subgroup (MenC-TT or MenC-CRM primed subjects)
	  ◦ Group 4: 25 subjects in each subgroup (MenC-TT or MenC-CRM primed subjects)
	• To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine in toddlers
	• To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with Nimenrix® in toddlers
	• To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccine conjugated to the tetanus toxoid carrier protein during infancy

	• To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccine conjugated to the CRM_{197} protein carrier during infancy ***Safety*** To evaluate the safety profile of MenACYW conjugate vaccine and Nimenrix®.
Observational Endpoints:	***Immunogenicity*** • Antibody titers ≥ 1:8 and ≥ 1:128 against meningococcal serogroups A, C, Y, and W measured by rSBA assessed before and at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® • Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA before and at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® ***Safety*** • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination • Occurrence, time 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 [DC] and electronic case report form [CRF]) injection site reactions occurring up to 7 days 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 DC and CRF) systemic reactions occurring up to 7 days 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 Visit 2 after vaccination • Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study of SAEs, [redacted] throughout the trial
Planned Sample Size:	Approximately 918 subjects are planned to be enrolled : <u>Meningococcal Vaccine Naïve Subjects:</u> Group 1 (MenACYW conjugate vaccine): planned=306 Group 2 (Nimenrix®): planned=306 <u>MenC Primed Subjects:</u> Group 3 (MenACYW conjugate vaccine): planned=204 Group 4 (Nimenrix®): planned=102

Schedule of Study Procedures:	Vaccination All subjects will receive a single dose of either MenACYW conjugate vaccine or Nimenrix® on D0 (V01). Blood sampling All subjects will provide a pre-vaccination blood sample at V01 (D0) and a post-vaccination sample at V02 (30 to 44 days after vaccination at V01). Collection of safety data • 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 CRF. • The subject's parent/legally acceptable representative will record information in a DC about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to V02 (D30 + 14 days). SAEs will be reported throughout the duration of the trial. • In addition, the subject's parent/legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the trial. • Staff will contact subjects' parent/legally acceptable representative by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the DC up to V02 and to bring it back to V02 (D30 + 14 days). • The completed DC will be reviewed with the subject's parent/legally acceptable representative at V02 (D30 + 14 days).
Duration of Participation in the Trial:	The duration of each subject's participation in the trial will be approximately 30 to 44 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 milliliter (mL) dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients: Meningococcal capsular polysaccharides: Serogroup A ..... 10 micrograms (µg) Serogroup C ..... 10 µg Serogroup Y ..... 10 µg Serogroup W ..... 10 µg Tetanus toxoid protein carrier.....approximately 65 µg
Route:	Intramuscular (IM)
Batch Number:	To be determined

Control Product:	**Nimenrix**®: Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)
Form:	Powder in a vial and solvent, for reconstitution, in a pre-filled syringe
Composition:	Each 0.5 mL dose of Nimenrix® is formulated to contain: *Neisseria meningitidis* polysaccharides: Serogroup A..... 5 µg Serogroup C..... 5 µg Serogroup W-135 ..... 5 µg Serogroup Y..... 5 µg Tetanus toxoid protein carrier..... 44 µg Excipients: In the powder: Sucrose, Trometamol In the solvent: Sodium chloride, Water for Injection
Route:	IM
Batch Number:	To be determined
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) Aged 12 to 23 months on the day of the first study visit 2) Subjects have received all recommended standard-of-care non-meningococcal vaccinations according to his/her age as per local regulations. 3) Informed consent form (ICF) has been signed and dated by the parent/legally acceptable representative 4) Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures 5) Covered by health insurance if required by local regulations 6) Subjects have not received any meningococcal vaccine in the second year of life (i.e., from 12 months of age). 7) **For Inclusion in Groups 1 and 2:** Subjects must not have received any vaccination against meningococcal disease with either a trial vaccine or a licensed meningococcal vaccine (i.e., polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, Y, B; or any monovalent or bivalent meningococcal vaccine). 8) **For Inclusion in Groups 3 and 4:**Subjects must have previously received at least 1 dose of licensed monovalent meningococcal C conjugate (MenC) vaccine during infancy (i.e., before 12 months of age)
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) Participation in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure

	2) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after study investigational vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines 3) Receipt of immune globulins, blood or blood-derived products in the past 3 months 4) **For Groups 1 and 2 only:** Vaccination against meningococcal disease with either a trial vaccine or a licensed meningococcal vaccine (i.e., polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, Y, B; or any monovalent or bivalent meningococcal vaccine) 5) **For Groups 3 and 4 only:** Vaccination against meningococcal disease with either a trial vaccine or a licensed meningococcal vaccine (i.e., polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, Y, B; or any monovalent B meningococcal vaccine), except licensed monovalent meningococcal C conjugate (MenC) vaccination received during infancy 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) 7) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically 8) At high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease) 9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances 10) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine 11) Personal history of Guillain-Barré syndrome (GBS) 12) Verbal report of thrombocytopenia as reported by the parent/legally acceptable representative contraindicating intramuscular vaccination in the Investigator's opinion 13) Bleeding disorder or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion 14) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion

	15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided. 16) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 17) Identified as a 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) according to randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS). Two co-primary objectives will be evaluated. **Primary Objective 1: Non-inferiority testing after 1 dose of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy** The percentages of subjects who achieve an hSBA titer ≥ 1:8 for meningococcal serogroups A, C, Y, and W in toddlers who received MenACYW conjugate vaccine (Group 1 and Group 3) are non-inferior to the corresponding percentages in toddlers who received Nimenrix® (Group 2 and Group 4) 30 days post administration. Null hypothesis (H_0): $p_{(Men)} - p_{(Nim)} \leq -10\%$ Alternative hypothesis (H_1): $p_{(Men)} - p_{(Nim)} > -10\%$ where $p_{(Men)}$ and $p_{(Nim)}$ are the percentages of subjects who achieve an hSBA titer ≥ 1:8 in the MenACYW conjugate vaccine group and the Nimenrix® group, 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 percentages is > -10%, the inferiority assumption will be rejected. For the 4 non-inferiority hypotheses using the response rates (percentages of subjects who achieve an hSBA titer ≥ 1:8), the 95% CI will be stratified on the priming status (meningococcal vaccine naïve or primed monovalent MenC vaccination during infancy) and calculated using the Wald method (normal approximation). Weighted average of the difference over strata will be calculated using the Minimal Risk weights with the null variance method. The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

	Primary Objective 2: Non-inferiority testing after 1 dose of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix®, the percentages of subjects who achieve an hSBA titer ≥ 1:8 for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2. Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$ Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$ where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA titer ≥ 1:8 in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages is > -10%, the inferiority assumption will be rejected. For the 4 non-inferiority hypotheses using the response rates (percentages of subjects who achieve an hSBA titer ≥ 1:8), 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. To conclude, non-inferiority in toddlers who either are meningococcal vaccine-naïve or have received monovalent MenC vaccination during infancy and non-inferiority in meningococcal vaccine-naïve subjects have to be demonstrated. **Secondary Objectives** No hypotheses will be tested. Descriptive statistics will be presented. <u>Secondary Objective 1</u> Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy, the hSBA geometric mean titer ratio (GMTR) between MenACYW conjugate vaccine or Nimenrix® will be calculated, and 95% CI will be provided. The 95% CI of the ratio of post-vaccination GMTs will be stratified on the priming vaccination status (meningococcal vaccine naïve or primed monovalent MenC vaccination) and calculated using an analysis of variance (ANOVA) model of $\log_{10}$-transformed titers. <u>Secondary Objective 2</u> Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers, the hSBA GMTR between MenACYW conjugate vaccine or Nimenrix® will be calculated, and 95% CI will be provided. <u>Secondary Objective 3</u> Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccination during infancy, the hSBA GMTR between MenACYW conjugate vaccine or Nimenrix® will be calculated, and 95% CI will be provided.

	Observational Objectives ***Immunogenicity*** Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Nimenrix®. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed. Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Nimenrix® treatment groups. In summary, descriptive analyses on A, C, Y, and W serogroups will include but not be limited to: • hSBA GMT and 95% CI at D0 and D30 • hSBA titer distribution and RCDC • Percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and 95% CI at D0 and D30 • Percentage of subjects with hSBA titer ≥4-fold rise from pre-vaccination to post-vaccination, and 95% CI • hSBA vaccine seroresponse* rate and 95% CI • rSBA† GMT and 95% CI at D0 and D30 • rSBA† titer distribution and RCDC • Percentage of subjects with rSBA† titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • rSBA† vaccine seroresponse‡ rate and 95% CI • Percentage of subjects with rSBA† titer ≥ 1:8 and ≥ 1:128 and 95% CI at D0 and D30 *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 that the pre-vaccination titer. † in a subset of subjects per group: 100 subjects each in Group 1 and Group 2; 50 subjects in each subgroup in Group 3 (MenCC-TT or MenC-CRM primed subjects); 25 subjects in each subgroup in Group 4 (MenC-TT or MenC-CRM primed subjects) ‡rSBA vaccine seroresponse 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. ***Safety*** Safety results will be described for subjects in each study groups. The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method).

Calculations of Sample Size

[redacted]

[redacted]

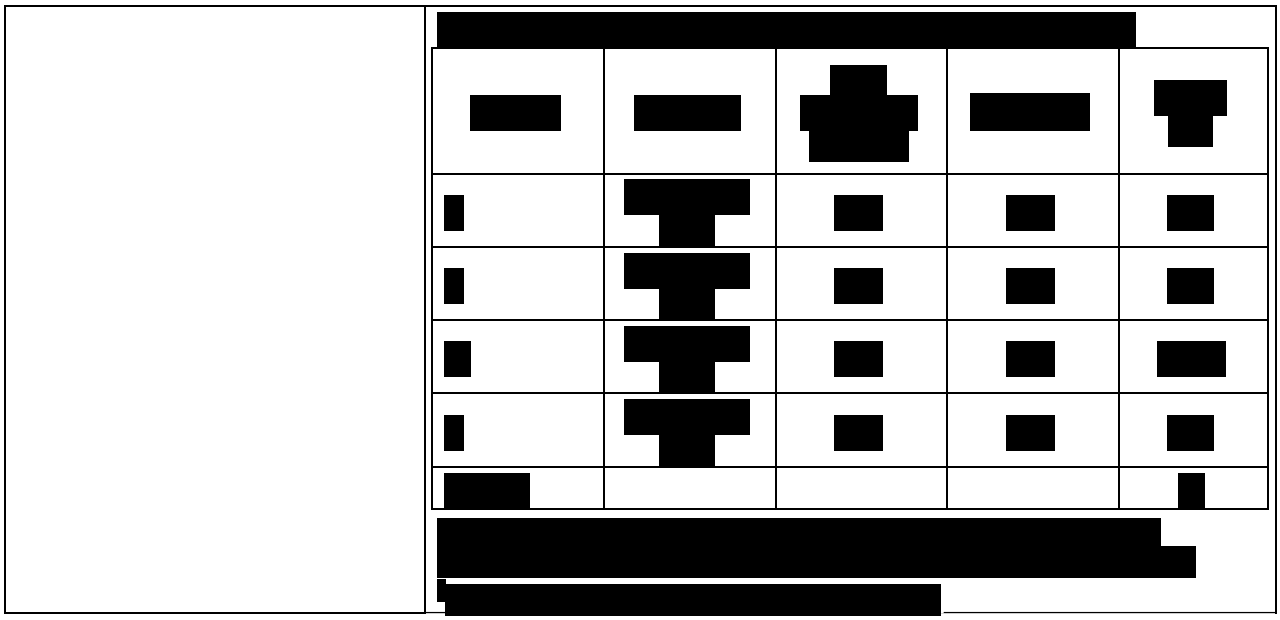

Table of Study Procedures

Phase III Trial, 2 Visits (V), 1 Telephone Call (TC), 1 Vaccination, 2 Blood Samples (BLs), 30 to 44 Days Duration per Subject

Visit/Contact	V01	TC	V02
Trial timelines (days)	D0	D08	D30
Time windows (days)	-	+2 days	+14 days
Informed consent form	X		
Inclusion/exclusion criteria*	X		
Collection of demographic data	X		
Medical history	X		
Collection of MenC vaccination history†	X		
Physical examination	X		
Review of temporary contraindications for blood sampling‡			X
Randomization/allocation of subject number	X		
Blood sample, 5 mL§	BL1		BL2
Study Vaccination**	X		
Immediate surveillance (30 minutes)	X		
DC provided	X		
TC		X††	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited AEs	D0 to V02		
Reporting of SAEs ([redacted]	To be reported throughout the study period		
DC reviewed and collected			X
Collection of reportable concomitant medications	X		X
Termination record			X

*Temperature needs to be measured by oral, rectal, or axillary route (axillary preferred) and recorded in the source document.

†Documentation of MenC vaccination during infancy will be collected for subjects who will be randomized to Group 3 or Group 4.

‡ 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 the appropriate timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

§ Blood sample at V01 will be drawn before administration of the vaccine

** Subjects will receive 1 dose of MenACYW conjugate vaccine or Nimenrix®.

†† This call is made 8 to 10 days after the vaccination at V01. If D08 (+2 days) falls on a weekend or holiday, the TC may be made on the following business day. During this TC, the staff will find out whether the subject experienced any SAE, [redacted], not yet reported, and will remind the subject's parent/legally acceptable representative to continue using the DC up to V02, to bring the DC to the study center at V02, and confirm the date and time of V02 (D30 + 14 days).

[redacted]

List of Abbreviations

µg	microgram
µL	microliter
AE	adverse event
[redacted]	[redacted]
ANOVA	analysis of variance
AR	adverse reaction
CDM	Clinical Data Management
CFU	colony-forming unit
CI	confidence interval
C&MQO	Clinical and Medical Quality Operations
CRA	Clinical Research Associate
CRF	case report form (electronic)
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	Day
DC	diary card
EDC	electronic data capture
EEA	European Economic Area
eSAE	electronic Serious Adverse Event (Form)
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global PharmacoVigilance
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IMD	invasive meningococcal disease
IOM	Institute of Medicine
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IWRS	interactive web response system
LCLS	last contact, last subject
LLOQ	lower limit of quantitation
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
mm	millimeter
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
PS	polysaccharides
PSO	Product Safety Officer
RCDC	reverse cumulative distribution curve
R&D	Research and Development
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SMT	safety management team
TC	telephone call
TMF	trial master file
UAR	unexpected adverse reaction
ULOQ	upper limit of quantitation
UTN	Universal Trial Number
V	Visit
WHO	World Health Organization

1 Introduction

1.1 Background

This trial will evaluate the immunogenicity and safety of a single dose of the quadrivalent Meningococcal Polysaccharide (Serogroups A, C, Y and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in toddlers 12 to 23 months of age who are either meningococcal vaccine naïve or have a background of vaccination with monovalent MenC vaccines during infancy. The purpose of MET51 is to demonstrate that the immunogenicity and safety profiles of the MenACYW conjugate vaccine are comparable with those of Nimenrix® in this age group.

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

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

Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in

2013-2014 compared with an average of 1% to 2% of all IMD cases in earlier years (24). A gradual increase in serogroup Y IMD has also been recently reported in Sweden during 2005-2012 (25) (26). Nearly 50% of all IMD was caused by serogroup Y in 2012 (25). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Scandinavian countries, accounting for 31% in Norway in 2009-2010 and 38% in Finland in 2010 (27).

The overall incidence rate of IMD in European Union (EU)/European Economic Area (EEA) countries was 0.68 per 100,000 (ranged from 0.11 to 1.77). The incidence per 100,000 in the study countries ranged from 0.72 in Spain to 0.52 in Hungary in 2012. The highest incidence rate of 5.10 per 100,000 was observed in children < 5 years of age in EU/EEA countries (28).

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: children as young as 6 weeks of age, adolescents, and adults including those 56 years of age and older.

1.2 Background of the Investigational Product

[redacted]

1.2.2 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 55 years of age; and MET32, a Phase I/II study in toddlers (29).

The final formulation has been evaluated in over 1639 subjects (infants, toddlers, adolescents, and adults > 55 years of age) in completed studies, MET39, MET44, MET50, and MET54. MenACYW conjugate vaccine is also being evaluated in an ongoing Phase III study (MET56 in adolescents). The relevant Phase II studies are discussed below.

MenACYW conjugate vaccine was found to be well tolerated and no unanticipated or new significant safety concerns have been identified in the clinical trials completed to date or in the ongoing MET56 study.

1.2.2.1 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® or Prevnar 13 vaccine, Pentacel®, ROTARIX® or RotaTeq®, hepatitis B vaccine, M-M-R®II, and VARIVAX®.

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.

After 1 dose of MenACYW conjugate vaccine at 12 months of age, the percentage of subjects achieving the protective hSBA threshold titer for serogroup A (75%) and serogroup C (90%) was similar to that obtained by subjects who received a primary series. Response rates were lower for serogroups Y and W (48% and 54%, respectively).

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 related SAEs during this study.

1.2.2.2 Study MET54 (Phase II)

MET54 was a Phase II, randomized, open-label, active-controlled, multi-center study conducted in Europe (Finland) in 2015. 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 200 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 rSBA and hSBA. MenACYW conjugate vaccine immune responses evaluated by rSBA and hSBA were generally comparable to Nimenrix® immune responses with some variation by serogroup:

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 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%).

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]).

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 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 findings were identified with administration of the 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 might be no direct benefit from receiving it. However, based on the data from previous studies, evaluation of the immunogenicity profile of MenACYW conjugate vaccine in different age groups shows that the majority of subjects develop seroprotective levels of antibodies after vaccination. The safety evaluation indicates that the vaccine is well-tolerated, and no safety issues have been detected to date. In all, the data support the further evaluation of MenACYW conjugate vaccine in humans.

Subjects who receive Nimenrix® will likely be protected against meningococcal disease caused by *N meningitidis* serogroups A, C, Y, and W.

As with any vaccine, MenACYW conjugate vaccine and Nimenrix® may not protect 100% of individuals against the disease they are designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine or Nimenrix® may cause injection site reactions such as pain, swelling, and erythema, or certain systemic events such as fever, irritability, drowsiness, loss of appetite, abnormal crying, and vomiting. There may be a rare possibility of an allergic reaction, which could be severe, and febrile convulsion in toddlers who experience high fever. There may be other risks for MenACYW conjugate vaccine that are not yet known.

[redacted] Importantly, no similar cases have been reported following the administration of MenACYW conjugate vaccine in any other completed trials.

Guillain-Barré syndrome (GBS) has been reported in older individuals, mostly in persons 11 through 19 years of age who had symptom-onset within 6 weeks of administration of a US-licensed meningococcal conjugate vaccine (30). 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 (31).

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 (32). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (32). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (33).

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

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

The potential risks listed here are not exhaustive; refer to the package insert of NIMERIX® (34) and the Investigator's Brochure of MenACYW conjugate vaccine for additional information regarding potential risks.

1.4 Rationale for the Trial

Three meningococcal C conjugate vaccines are currently licensed in European countries. The MenC conjugate vaccines are made from capsular polysaccharide that has been extracted from cultures of capsular group C *Neisseria meningitidis*. The polysaccharide is linked (conjugated) to a carrier protein, either CRM_{197} (a non-toxic variant of diphtheria toxin) or tetanus toxoid. The conjugation increases the immunogenicity, especially in young children in whom the plain polysaccharide vaccines are less immunogenic. The vaccination schedule and the number of vaccinations vary across the EU countries. Depending on the country, an infant may have received 1 to 2 doses of meningococcal C conjugate vaccine during the first year of life (35).

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 > 65 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 vaccine, Menactra®, the MenACYW conjugate vaccine is prepared by using tetanus toxoid as the carrier protein. Conjugation of PS 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 purpose of MET51 is to evaluate the quadrivalent meningococcal conjugate vaccine when used as a single-dose toddler vaccine in individuals who are either meningococcal vaccine naïve or have received one or more doses of monovalent MenC vaccines during infancy. The study will aim to demonstrate non-inferior immunogenicity of MenACYW conjugate vaccine versus Nimenrix® and evaluate the safety of 1 dose of MenACYW conjugate vaccine compared to 1 dose of Nimenrix® in toddlers 12 to 23 months of age who are either meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy.

2 Trial Objectives

2.1 Primary Objectives

1) To demonstrate the non-inferiority of the antibody response to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
2) To demonstrate the non-inferiority of the antibody response to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers

The endpoints for the primary objectives are presented in Section 9.1.1.1.

2.2 Secondary Objectives

1) To compare the antibody responses (geometric mean titers [GMTs]) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
2) To compare the antibody responses (GMTs) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in meningococcal vaccine naïve toddlers
3) To compare the antibody responses (GMTs) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in toddlers who received monovalent MenC vaccination during infancy

The endpoints for the secondary objectives are presented in Section 9.2.1.1

2.3 Observational Objectives

Immunogenicity

- To describe the antibody response to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after a dose of MenACYW conjugate vaccine or Nimenrix® in terms of rSBA titers ≥1:8 and ≥ 1:128 in toddlers in a subset of subjects per group:
    - Group 1 and Group 2: 100 subjects each
    - Group 3: 50 subjects in each subgroup (MenC-TT or MenC-CRM primed subjects)
    - Group 4: 25 subjects in each subgroup (MenC-TT or MenC-CRM primed subjects)
- To describe the antibody response to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine in toddlers

- To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with Nimenrix® in toddlers
- To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccine conjugated to the tetanus toxoid carrier protein during infancy
- To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccine conjugated to the CRM_{197} protein carrier during infancy

Safety

To evaluate the safety profile of MenACYW conjugate vaccine and Nimenrix®.

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

3 Investigators and Trial Organization

This trial will be conducted in approximately 32 to 40 centers in 4 or 5 countries in Europe. Approximately 35 trial centers in Spain, Hungary, Germany, and Finland will be included in the trial. Other countries may potentially be included if needed to complete enrollment. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator in each country. Details of the trial centers, the Investigators at each center, and the Coordinating Investigators are provided in the "List of Investigators and Centers Involved in the Trial" document.

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

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

4 Independent Ethics Committee/Institutional Review Board

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

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and/or the Sponsor are responsible for obtaining this approval and/or favorable opinion before the start of the trial. 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 and/or Sponsor will submit written summaries of the status of the trial to the IEC/IRB annually, or more frequently if requested as per local regulations.

SAEs occurring during the trial will be reported by the Investigator and/or Sponsor to the IEC/IRB, according to the IEC/IRB policy and to local regulatory requirements.

5 Investigational Plan

5.1 Description of the Overall Trial Design and Plan

5.1.1 Trial Design

This will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a single dose of MenACYW conjugate vaccine to a single dose of a licensed quadrivalent meningococcal polysaccharide groups A, C, W-135, and Y conjugate vaccine, Nimenrix®, in toddlers (12 to 23 months of age) in the EU who are either meningococcal vaccine naïve or received monovalent MenC vaccination during infancy.

Approximately 918 healthy toddlers aged 12 to 23 months will be enrolled and randomized as follows depending on the meningococcal background:

Meningococcal Vaccine-Naïve Subjects: 612 subjects will be randomized in a 1:1 ratio to the following 2 groups:

- Group 1: MenACYW conjugate vaccine (n=306)
- Group 2: Nimenrix® (n=306)

MenC-Primed Subjects: 306 subjects will be randomized in a 2:1 ratio to the following 2 groups:

- Group 3: MenACYW conjugate vaccine (n=204)
- Group 4: Nimenrix® (n=102)

Enrollment of MenC-primed subjects will be stratified by the type of primed vaccine, MenC-TT (NeisVac-C®) or MenC-CRM (Menjugate®, Meningitec®), considering that at least 25% and a maximum of 50% of subjects will have been primed with MenC-CRM as described in Table 5.1.

Table 5.1: MenC priming strategy

Priming	Group 3 MenACYW conjugate vaccine	Group 4 Nimenrix®
MenC-TT	102 - 152*	51 - 76*
MenC-CRM	52* - 102	26* - 51
Total	204	102

*Sample size corresponding to 25% of subjects primed with MenC-CRM

All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days post-vaccination.

Solicited adverse event (AE) information will be collected for 7 days after vaccination, unsolicited AE information will be collected from Visit (V) 01 (Day [D] 0) to V02 (D30 [+14 days]), and serious adverse event (SAE) information, [redacted] will be collected throughout the trial.

5.1.2 Justification of the Trial Design

[redacted] MET51 is a study that will be conducted as part of the Phase III of development of the MenACYW conjugate vaccine in which the vaccine would be evaluated in the age group 12 to 23 months of age. This age group has been selected since the rates of meningococcal disease are highest in young children with a secondary peak in adolescents and young adults aged 11 to 19 years (36).

This study is designed to evaluate the immunogenicity responses and safety profiles following the administration of a single dose of the MenACYW conjugate vaccine in toddlers 12 to 23 months of age who either are meningococcal naïve or have received monovalent MenC vaccination during infancy.

Data in toddlers who have previously received MenC during infancy are needed as part of the overall data required by the European Medicines Agency (EMA) in the context of achieving licensure with a broad age indication. These data will be complementary to the data generated in this study in meningococcal vaccine-naïve toddlers as well as in the MET54 study where MenC-naïve toddlers in the EU were randomized either to receive a single dose of MenACYW conjugate vaccine or Nimenrix®. The MET51 study collects data about the MenC conjugate vaccine administered to the study subjects during their first year of life (either TT protein as conjugate or CRM_{197} protein as conjugate); descriptive analysis is planned as a part of the observational objectives in this study to account for this difference in the background vaccination.

Since the primary objectives of this study have serological endpoints and the vaccines for the study groups have different appearances, the study has a modified double-blind design. This means it contains an unblinded vaccine administrator while the rest of the study team, including laboratory technicians in charge of executing the serological testing, remain blinded to the subjects' group allocations throughout the entire study up to the database lock to avoid any bias.

The unblinded site personnel, who will not participate in any safety evaluation of the subjects during study conduct, will prepare all vaccines, and then administer the vaccines to the subjects.

5.1.3 Trial Plan

Eligible subjects will be identified and recruited.

A schedule of assessments and study vaccinations is provided in the Table of Study Procedures.

Vaccination

All subjects will receive a single dose of either MenACYW conjugate vaccine or Nimenrix® on D0 (V01).

Blood Sampling

All subjects will provide a pre-vaccination blood sample at V01 (D0) and a post-vaccination sample at V02 (30 to 44 days after vaccination at V01).

Collection of safety data

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 electronic case report form (CRF) (see Section 9.3.2.3.1).

The subjects' parent/legally acceptable representative will record information in a diary card (DC) about solicited reactions from D0 to D07 after vaccination and unsolicited AEs only from D0 to V02 (D30 + 14 days). SAEs will be reported throughout the duration of the trial.

In addition, the subject's parent/legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the trial.

Staff will contact the subject's parent/legally acceptable representative by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the DC up to V02 and to bring it back to V02 (D30 + 14 days).

The completed DC will be reviewed with the subject's parent/legally acceptable representative at V02 and collected at V02 (D30 + 14 days).

5.1.4 Visit Procedures

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

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

1) Give the subject's parent/legally acceptable representative information about the trial, answer any questions, obtain signed informed consent, and give him/her a signed copy.
2) Check inclusion and exclusion criteria for eligibility.
3) Take the subject's temperature (axillary, rectal, or oral, but axillary preferred) and record in the source document.
4) Collect demographic data.

5) Obtain verbal medical history about the subject.

6) Review vaccination history from the child's immunization record. For subjects who will be randomized to Group 3 or Group 4, record meningococcal vaccination history from the child's immunization record, including MenC vaccination history during infancy, the number of doses, the date(s) received, and the brand name of the product received.

7) Perform a physical examination, including but not limited to examination of the head (including ear, nose, and throat), neck, thorax (including heart and lungs), abdomen, and extremities. If a routine examination had been performed within the last month by the Investigator, a sub-investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area.

8) Connect to the Interactive Web Response System (IWRS) for subject identification and randomization.

9) Obtain the first 5-milliliter (mL) blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).

10) Administer the appropriate study vaccine IM in the anterolateral area of the thigh or the deltoid muscle of the upper arm according to country specific recommendations and according to the study group listed below:

    Group 1 and Group 3 = MenACYW conjugate vaccine

    Group 2 and Group 4 = Nimenrix®

11) Keep the subject under observation for 30 minutes and record any AE in the source document.

12) Give the parent/legally acceptable representative a diary card, a thermometer, and a ruler, and go over the instructions for their use.

13) Remind the parent/legally acceptable representative to expect a telephone call (TC) 8 days (+2 days) after V01 (D0) and to bring back the DC when they return for V02 (D30 + 14 days).

14) Remind the parent/legally acceptable representative to notify the site in case of an SAE.

15) Complete the relevant CRF pages for this visit.

TC (8 days [+2 days] after Visit 1)

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

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.

2) Remind the parent/legally acceptable representative to do the following:
    - Complete the D0 to D07 pages of the DC.
    - Complete the remaining pages of the DC, and bring them to V02 (D30 + 14 days).

- Notify the site in case of an SAE

3) Confirm the date of the next visit.

V02 (D30 [+14 days] after V01): Collection of Safety Information and Blood Sample

1) Review the pages of the DC with the parent/legally acceptable representative, including any AEs, medications, or therapy that occurred since vaccination. The parent/legally acceptable representative must return the DC.
2) Review temporary contraindications for V02 blood sampling (see Section 5.2.8).
3) Obtain the second 5 mL blood sample (see Section 7 for detailed instructions regarding the handling of blood samples).
4) Complete the termination record of the CRF, and enter the subject's termination information in the IWRS
5) If the subject or the subject's parent/legally acceptable representative does not return for V02 and the DC is not received at the site, site personnel will contact the subject or the subject's parent/legally acceptable representative by telephone. During the telephone call, the subject or the subject's legally acceptable representative will be reminded to return the DC to the study site. Telephone calls will be documented on the Telephone/Interview Record. If the study personnel are unable to contact the subject or the subject's parent/legally acceptable representative with 3 attempts, the study personnel will follow instructions given in Section 5.2.10.

SAEs and AEs That Are Related to Vaccination or That Led to Discontinuation:

At any time during the study, a subject who experiences an SAE or an AE must be followed if *either* of the following is true:

- The SAE or AE is considered by the Investigator to be related to vaccination, and is not resolved by the end of the subject's participation in the trial
- The subject has been discontinued from the trial because of the SAE or AE

Any such subject must be followed until the condition resolves, becomes stable, or becomes chronic.

5.1.5 Planned Trial Calendar

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

Planned trial period - FVFS (first visit, first subject) to LCLS (last contact, last subject): 1Q 2017 to 4Q 2017

Planned inclusion period - FVFS to FVLS (first visit, last subject): 1Q 2016 to 4Q 2017

Planned end of trial[a]: 4Q 2017

Planned date of final clinical study report: 4Q 2018

5.1.6 Early Safety Data Review

This trial will not include an early review of safety data (i.e., no early safety reviews of preliminary safety data occurring at pre-determined milestones defined in the protocol with pause in enrollment). However, it 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 the countries where the trial is taking place.

If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the subjects' parents/legally acceptable representative and should assure appropriate therapy and follow-up.

5.2 Enrollment and Retention of Trial Population

5.2.1 Recruitment Procedures

Before the start of the trial, the Investigator or sub-investigator may contact the parents/legally acceptable representatives of an appropriate pool of potential subjects and invite them to participate in the trial. The site will ensure that any advertisements used to recruit subjects (e.g. letters, pamphlets, posters) are submitted to Sanofi Pasteur before submission to the IEC/IRB for approval.

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

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject's parent/legally acceptable representative voluntarily confirms his or her willingness to let his/her child participate in a particular trial. 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's parent or legally acceptable representative must be informed by appropriate study personnel about all aspects of the trial that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

A subject whose parent/legally acceptable representative cannot read or who cannot read the native language of the country will not be included in the trial.

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[a] The end of the trial is defined as the date of the last contact with a subject i.e., 4Q 2017

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 parent's/legally acceptable representative's willingness to continue participation in the trial, 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.

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's parent/legally acceptable representative.

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

Rationale for Including Subjects Unable to Give Consent:

MET51 is a study to be conducted in toddlers 12 to 23 months of age to obtain safety and immunogenicity data in this age group (see Section 1.4).

Since these subjects are unable to give their consent, written informed consent must be obtained from the parent or legally acceptable representative in accordance with local practices before participation in the study and before any study-related procedure is done. The signature on the ICF must be dated by the parent/legally acceptable representative in accordance with local practices. The parent/legally acceptable representative should be able to consent for their child. The child of minor parents must not be included in the study.

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 in order to be eligible for trial enrollment:

1) Aged 12 to 23 months on the day of the first study visit[a].
2) Subjects have received all recommended standard-of-care non-meningococcal vaccinations according to his/her age as per local regulations.
3) ICF has been signed and dated by the parent/legally acceptable representative.
4) Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures.
5) Covered by health insurance if required by local regulations.

[a] "12 to 23 months" means from the 12th month after birth to the day before the 24th month after birth.

6) Subjects have not received any meningococcal in the second year of life (i.e., from 12 months of age).
7) **For Inclusion in Groups 1 and 2:** Subjects must not have received any vaccination against meningococcal disease with either a trial vaccine or a licensed meningococcal vaccine (i.e., polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, Y, B; or any monovalent or bivalent meningococcal vaccine).
8) **For Inclusion in Groups 3 and 4:** Subjects must have previously received at least 1 dose of licensed monovalent meningococcal C conjugate (MenC) vaccine during infancy (i.e., before 12 months of age)

5.2.5 Exclusion Criteria

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

1) Participation in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
2) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after study investigational vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.
3) Receipt of immune globulins, blood or blood-derived products in the past 3 months
4) **For Groups 1 and 2 only**: Vaccination against meningococcal disease with either a trial vaccine or a licensed meningococcal vaccine (i.e., polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, Y, B; or any monovalent or bivalent meningococcal vaccine)
5) **For Groups 3 and 4 only**: Vaccination against meningococcal disease with either a trial vaccine or a licensed meningococcal vaccine (i.e., polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, Y, B; or any monovalent B meningococcal vaccine), except licensed monovalent meningococcal C conjugate (MenC) vaccination received during infancy.
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)
7) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically
8) At high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease)

9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[a]
10) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine
11) Personal history of Guillain-Barré Syndrome (GBS)
12) Verbal report of thrombocytopenia, as reported by the parent/legally acceptable representative contraindicating intramuscular vaccination in the Investigator's opinion
13) Bleeding disorder or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion
14) Chronic illness[b] that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion
15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
16) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
17) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

Depending on local or country regulations, if the subject has a primary physician who is not the Investigator, the site must contact this physician with the consent of the subject's parent / legally acceptable representative to inform him/her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant medical history (reported as diagnosis) including conditions for which the subject is or has been followed by a physician or conditions 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 CRF. The significant medical history section of the CRF 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.

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[a] The components of the MenACYW conjugate vaccine are listed in Section 6.1.1.1 and the Investigator's Brochure. The components of the Nimenrix® are listed in Section 6.1.2.1 and the package insert.

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, autoimmune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases.

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 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 trial.

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable since only 1 dose of vaccine will be administered in this trial.

5.2.8 Contraindications for Visit 2 Blood Sample

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 the appropriate timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.9 Conditions for Withdrawal

Parents/Legally acceptable representatives will be informed that they have the right to withdraw their child from the trial at any time. A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject's permission.
- At the request of the subject's parent/legally acceptable representative (dropout).

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

- Significant non-compliance with the protocol, based on the Investigator's judgment.

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

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

Withdrawn subjects will not be replaced.

5.2.10 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (i.e., documented telephone calls and certified mail) should be undertaken to locate or recall

them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the CRF and in the source documents.

5.2.11 Classification of Subjects Who Discontinue the Trial

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

- **Serious adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an SAE, as defined in Section 9.3.2.1.
- **Other adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an AE other than an SAE, as defined in Section 9.3.2.1.
- **Non-compliance with protocol:** To be used when the Investigator withdraws a subject from the study because of failure to follow the protocol, including when it is retrospectively discovered that a subject did not fulfill the eligibility criteria. The Investigator will provide a comment as to the specific cause of non-compliance.
- **Lost to follow-up:** To be used when the Investigator withdraws a subject from the study because of failure to establish contact, as outlined in Section 5.2.10. The Investigator will provide documentation that contact was attempted (i.e., return of unsigned certified letter receipt).
- **Voluntary withdrawal not due to an adverse event:** To be used when a subject drops out of the study for any reason other than those listed above.

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 trial because of an SAE, other type of AE, non-compliance with the protocol, or loss of eligibility, including definite 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.

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 trial 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 Global PharmacoVigilance (GPV) (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 Trial and Protocol

Any amendments to this trial plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments, e.g., that affect the conduct of the trial 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 or logistical aspect of the trial but does not affect its design or objectives or have an impact on the subjects' safety. The IECs/IRBs also need only be notified if an administrative amendment is made, according to local regulations.

The Investigator is responsible for ensuring that changes to an approved trial, 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 Trial

The trial may be discontinued if new data about the investigational product resulting from this or any other trials become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, and/or the IECs/IRBs. If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the regulatory authorities, and the IECs/IRBs of the reason for termination or suspension, as specified by the applicable regulatory requirements.

The Investigator shall promptly inform the trial subjects and assure appropriate therapy and/or follow-up for them.

6 Vaccines Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Trial 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 supplied in vials
Dose: 0.5 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 65 µg

6.1.1.2 Preparation and Administration

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

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

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

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

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

6.1.1.3 Dose Selection and Timing

All subjects in Group 1 and Group 3 will receive 1 dose of MenACYW conjugate vaccine at V01 (D0).

6.1.2 Identity of Control Product

Nimenrix®: Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)

Form: Powder in a vial and solvent, for reconstitution, in a pre-filled syringe
Dose: 0.5 mL
Route: IM
Batch number: Commercial lot to be supplied by Sponsor

6.1.2.1 Composition

Each 0.5 mL dose of Nimenrix® is formulated to contain:

N meningitidis polysaccharides:
- Serogroup A.....5 µg
- Serogroup C.....5 µg
- Serogroup Y.....5 µg
- Serogroup W-135.....5 µg

Tetanus toxoid protein carrier .....44 µg

Excipients:
- In the powder: Sucrose, Trometamol
- In the solvent: Sodium chloride, Water for injection

6.1.2.2 Preparation and Administration

Nimenrix® is supplied as a white powder in a glass vial, together with a clear and colorless solvent supplied in a pre-filled (0.5mL) syringe. The supplied solvent is used to reconstitute the powder in the vial.

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 procedures for administering Nimenrix® are the same as those described for the trial product in Section 6.1.1.2. See the Nimenrix® EU Summary of Product Characteristics (34) for detailed information.

6.1.2.3 Dose Selection and Timing

All subjects in Group 2 and Group 4 will receive 1 dose of Nimenrix® on V01 (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 with the required information according to national regulations.

Commercial lots of Nimenrix® will be supplied by Sanofi Pasteur Inc. and labeled with the required information according to national regulations.

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 in order to determine the dates and times of delivery of products.

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

6.3.2.2 Product Storage

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

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

6.3.2.3 Product Accountability

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

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

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

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

6.3.3 Replacement Doses

MenACYW conjugate vaccine and Nimenrix®

If a replacement dose is required (e.g., because the vial broke or particulate matter was observed in the vial), the site personnel must either connect to the IWRS to receive the new dose allocation, or follow the instructions given in the Operating Guidelines. The unblinded site personnel must connect to the IWRS 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 either disposed of or returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the trial period.

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigators will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

The MET51 trial is modified double-blind, which means that both the subject and the Investigator remain unaware of the treatment assignments throughout the trial. 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 trial until database lock.

The code may be broken by the Investigator only in the event of an SAE and if identification of the vaccine received could influence the treatment of the SAE. Code-breaking should be limited, as far as possible, to the subject experiencing the SAE.

The blind can be broken by the Investigator or a sub-investigator (medical doctor only[a]), by connecting to the IWRS system as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator 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.

[a] according to local regulations

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

- by GPV department for reporting to Health authorities in the case of an SAE as described in International Conference on Harmonisation (ICH) E2A.[a] In this case, the code will be broken only for the subject in question. The information resulting from code-breaking (i.e., 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.

6.5 Randomization and Allocation Procedures

Each 12 to 23 month old toddler whose parent/legally acceptable representative signs the ICF, and who meets the inclusion/exclusion criteria will be randomly assigned via IWRS to Group 1 and Group 2 for the meningococcal vaccine-naïve subjects according to a 1:1 ratio and to Group 3 and Group 4 for the MenC-primed subjects according to a 2:1 ratio. Site staff will connect to the IWRS, enter the identification and security information, and confirm a minimal amount of data in response to IWRS prompts. The IWRS will then provide the group assignment and have the caller confirm it. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the trial, the information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IWRS will consist of an 8-digit string (a 3-digit trial center identifier and a 5-digit subject identifier connected by "-"). For example, Subject 001-00001 is the first subject enrolled in center number 1.Subject numbers should not be reassigned for any reason.

6.6 Treatment Compliance

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

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

[a] All unexpected and related SAEs submitted to European Community Competent Authorities must be unblinded.

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications including other therapies e.g., blood products, should be recorded in the source document as well as new medications prescribed for new medical conditions/AEs during trial participation.

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

Reportable medications will be collected in the CRF from the day of vaccination to the end of the solicited and unsolicited follow-up period (e.g., 30 day safety follow-up) as they may impact the response to the vaccination and impact the consistency of the information collected on concomitant medications at any vaccination.

The "reportable" medications are distributed according to 3 categories. These are:

- Category 1 antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immune modulators.

Note: inhaled and topical steroids should not be captured.

- Category 2: Reportable medications used to define the Per-Protocol Analysis Set (PPAS). For example:
    - Influenza and other non-study vaccine: influenza vaccine in the 2 weeks (14 days) preceding the trial vaccination up to the subject's termination from the trial and any other vaccines (other than study vaccine) in the 4 weeks (28 days) preceding the trial vaccination up to the subject's termination from the trial.
    - Immune globulins, blood, or blood-derived products: used in the 3 months preceding the first blood draw and up to the subject's termination from the trial.
    - Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy: used in the 6 months preceding the trial vaccination and up to the subject's termination from the trial.
- Category 3: Oral or injectable antibiotics, which may interfere with bioassays used for antibody testing when taken before a blood draw.
    - The period of collection should be within 3 days before the first blood draw and up to the last scheduled blood draw.

Note: Inhaled and topical antibiotics (drops, creams, or ointments) should not be captured.

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

- Trade name
- Given as treatment or as prophylaxis
- Medication category
- Start and stop dates

Dosage and administration route will not be recorded. Homeopathic medication will not be recorded. Topical treatment will not be recorded.

The fact that a medication was given in response to an AE will be captured in the "Action Taken" column of the AE only. No details will be recorded in the concomitant medication module of the CRF unless the medication received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at Visits 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 Visits 1 and 2, 5 mL of blood will be collected by staff experienced in blood collection in a pediatric population 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 verify 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.

If attempts to obtain the first blood draw are unsuccessful (after reasonable attempts as per local regulations) then Visit 1 can be rescheduled to a later date at which point inclusion/exclusion criteria must be re-validated. If during the rescheduled visit the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.

7.2 Sample Preparation

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

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

The samples are then centrifuged, and the separated serum is transferred to the appropriate number of aliquoting tubes by pipetting; samples are handled 1 subject at a time to avoid the mix-up of the subjects' blood tubes. At least 1.5 mL of serum should be placed in the primary cryotube, and the remaining sera should be placed in the retention cryotubes. If less than 1.5 mL of serum is available, all of the sera should be placed in the primary cryotube, and no retention cryotubes should be used. 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 trial. 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 International Air Transport Association (IATA) 602 regulations.

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

All assays will be performed at GCI, Sanofi Pasteur Inc., Swiftwater, PA, USA or at a GCI qualified contract laboratory.

7.4 Future Use of Stored Serum Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 5 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

Depending upon local regulations, the subject's parents/legally acceptable representatives 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 laboratory methods. Genetic tests will never be performed on these samples.

8 Clinical Supplies

Sanofi Pasteur will supply the trial sites with protocols, ICFs, CRFs, SAE reporting forms, diary cards, and other trial documents, as well as with the following trial materials: MenACYW conjugate vaccine, Nimenrix®, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

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

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. They must allow approximately 1 week for an order to be filled and to have the supplies sent to their site.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

1) Antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
2) Antibody titers.≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers

9.1.1.2 Immunogenicity Assessment Method

[redacted]

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the trial.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

The secondary endpoints for immunogenicity are:

1) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
2) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers
3) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccination during infancy

9.2.1.2 Immunogenicity Assessment Methods

Antibodies to meningococcal antigens (hSBA method)

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

This method will be performed on all blood samples (BL1 and BL2) for all study groups.

9.2.2 Safety

There are no secondary objectives for safety.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the trial.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 Immunogenicity Endpoints

The observational endpoints for immunogenicity are:

- Antibody titers ≥ 1:8 and ≥ 1:128 against meningococcal serogroups A, C, Y, and W measured by rSBA assessed before and at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix®
- Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix®.

9.3.1.2 Immunogenicity Assessment Methods

[redacted]

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

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

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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient'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[d]

Adverse Reaction:

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

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

Unexpected Adverse Reaction (UAR):

An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

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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 Serious Adverse Events, with the exception of: hospitalization planned before inclusion into the study or out-patient treatment with no hospitalization.

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

[d] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events 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 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, GBS, new onset diabetes, or autoimmune disease.

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the CRF**.** The assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of:

- Symptom and
- Onset post-vaccination

Examples of solicited reactions include injection site tenderness, redness, swelling between D0 and D07 post-vaccination, or irritability between D0 and D07.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and/or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D07 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D07 is a solicited reaction, whereas headache starting on D08 post-vaccination is an unsolicited AE.

An unsolicited non-serious AE is an unsolicited AE excluding SAEs.

Injection Site Reaction:

An injection site reaction[a] is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions.

Systemic AE:

Systemic AEs are all AEs that are not injection 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 site, e.g., erythema that is localized but that is not at the injection site.

[redacted]

[redacted]

[a] All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

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 electronic CRF) injection site reactions occurring up to 7 days 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 CRF) systemic reactions occurring up to 7 days 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 Visit 2 after vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study of SAEs, [redacted], throughout the trial.

9.3.2.3 Safety Assessment Methods

At V02, the Investigator or a delegate will ask the subject's parent/legally acceptable representative 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 CRF according to the instructions provided by the Sponsor.

9.3.2.3.1 Immediate Post-vaccination Surveillance Period

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

- Any unsolicited systemic AE occurring during the first 30 minutes post-vaccination will be recorded on the CRF as immediate unsolicited systemic AE.
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded and analyzed as starting on the day of vaccination.
- Any SAE occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10.

9.3.2.3.2 Reactogenicity (Solicited Reactions from D0 to D07 after Vaccination)

After vaccination, subject's parent/legally acceptable representative will be provided with a safety diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subject's parent/legally acceptable representative in the diary card on the day of vaccination and for the next 7 days (i.e., D0 to D07) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event, if any (e.g., medication)

The action taken by the subject's parent/legally acceptable representative to treat any solicited reactions will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

4: Hospitalization (inpatient)

Subject's parents/legally acceptable representatives will be contacted by telephone 8 days (+2 days) after vaccination to remind them to record all safety information in the diary card.

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

Table 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRF, together with the intensity scales.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Injection site tenderness	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition		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: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3: Cries when injected limb is moved, or the movement of the injected limb is reduced	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 tenderness, parents/legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA LLT)	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥ 38.0°C	Vomiting does not include spitting up	Inconsolable crying without a reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.5°C	Grade 1: 1 episode per 24 hours	Grade 1: < 1 hour	Grade 1: Sleepier than usual or less interested in surroundings	Grade 1: Eating less than normal	Grade 1: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C	Grade 2: 2–5 episodes per 24 hours	Grade 2: 1–3 hours	Grade 2: Not interested in surroundings or did not wake up for a feed/meal	Grade 2: Missed 1 or 2 feeds/meals completely	Grade 2: Requiring increased attention
	Grade 3: > 39.5°C	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds/meals or refuses most feeds/meals	Grade 3: Inconsolable

* For all reactions but fever, parents/legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Important notes for the accurate assessment of temperature:

Parents/legally acceptable representatives 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 DC, and the highest temperature will be recorded by the site in the CRF. The preferred route for this trial is axillary. The same route should be used to collect all temperature measurements from the subject. 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 Non-serious Adverse Events from D0 to Day 30 after Vaccination

In addition to recording solicited reactions, parents/legally acceptable representatives 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.

For each unsolicited non-serious AE, the following information is to be recorded:

- Start and stop dates[a]
- Intensity of the event:
  - For measurable unsolicited non-serious AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.1 and Table 9.2)
  - Other unsolicited non-serious AEs will be classified according to the following intensity scale:
    - Grade 1: No interference with activity
    - Grade 2: Some interference with activity
    - Grade 3: Significant; prevents daily activity
- Action taken for each AE, if any (e.g., medication)

The action taken by the parent/legally acceptable representative to treat any **unsolicited AEs** will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

[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 trial will be considered as ongoing at the end of the trial.

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

- Whether the AE led to discontinuation
- Whether the AE was related to vaccination (for unsolicited systemic AEs)

9.3.2.3.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from inclusion until 30 days (+14 days) after vaccination.

Any SAE occurring at any time during the trial will be reported by the Investigator through the EDC system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE is to be reported, either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). The Investigator will assess the causal relationship between the SAE and the investigational product as either "Not related" or "Related", as described in Section 10.4.

See Section 10 for further details on SAE reporting.

9.3.2.3.5 [redacted]

[redacted] (37)

[redacted]

9.3.2.3.6 Assessment of Causality

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

0: Not related – The AE is clearly/most probably caused by other etiologies such as subject's 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)

1: Related – There is a "reasonable possibility" that the AE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all injection site AEs (solicited and unsolicited) and all solicited systemic reactions are considered to be related to vaccination and referred to as reactions, and therefore 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 trial 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.

9.3.3 Efficacy

No clinical efficacy data will be obtained in the trial.

10 Reporting of Serious Adverse Events

In order 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 (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed into the electronic Serious Adverse Event (eSAE) Form.

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the trial or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The SAE form must be signed by a

[a] ICH Guidelines, Clinical Safety Data Management E2A

licensed physician (M.D. or D.O.) for whom the task is listed on the Study Task Delegation and Signature List after each update to the Form.

The Investigator must complete the "eSAE Form" in the EDC application. After validation, an e-mail alert will automatically be sent to the GPV mailbox, the CRA and the CTL. This message will include the country, the study code, the subject number, whether the report is initial or a follow-up, the diagnosis and/or symptoms, the seriousness criteria, the relationship, if related, and the outcome, if fatal.

If the EDC system is unavailable, the site must notify the Sponsor using the paper version of the SAE Reporting Form, as follows:

The Investigator must complete the SAE Reporting Form, check off the "Initial Reporting Form" box, and send it to the Sponsor by one of the following means (preferably by fax or e-mail):

- 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] (see the Operating Guidelines for directions on how to send a password-protected email)
- By express mail, to the following address: Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global Pharmacovigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370

When the system becomes available, the Investigator must transcribe the information from the paper version of the eSAE Form into the EDC system.

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

10.2 Follow-up Reporting by the Investigator

The eSAE Form completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). After validation, an e-mail alert will be sent automatically to the GPV Department and to the CRA. All relevant information must be included directly in the eSAE form. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the GPV Department.

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

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

Any SAE that occurs after a subject has completed the study but that is likely to be related to the product 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 will first be evaluated by the Investigator, using the following definitions:

> **0 - 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 SAE is incompatible with a causal relationship; or the SAE started before the vaccination (screening phase, if applicable).
>
> **1 - Related**: There is a "reasonable possibility" that the SAE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship.
>
> *(ICH Guidelines, Clinical Safety Data Management E2A)*

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

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

10.5 Reporting SAEs to Health Authorities and IECs/IRBs

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

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

11 Data Collection and Management

11.1 Data Collection and CRF Completion

Individual safety diary cards, specifically designed for this trial by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.3.2.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Parents/Legally acceptable representatives 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 parents/legally acceptable representatives on how to correctly use these tools.

Relevant information will be transcribed into the CRF. Any SAEs, [redacted], captured during this 30-day follow-up period will be reported and followed-up as per the normal process for reporting SAEs.

At specified intervals, the Investigator or an authorized designee will interview the parents/legally acceptable representatives to collect the information recorded in the DC, and will attempt to clarify anything that is incomplete or unclear. All clinical trial information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRF. (Any information that was not documented in the DC will first be captured in the source document and then reported electronically.) The CRF has been designed specifically for this trial 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 CRFs, 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 guidelines will be provided to assist with data entry during the course of the trial.

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 trial 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 trial 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 in order to track all modifications and to ensure database integrity.

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

11.2 Data Management

Management of Clinical Data

Data generated during the trial will be managed following 2 different processes:

- Clinical data, defined as all data reported in the CRF, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.
- Data pertaining to SAEs, which are reported by the Investigator on the eSAE Forms or SAE Reporting Forms, will be handled by the Sponsor's GPV Department.

During the trial, clinical data reported in the CRFs 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 in order to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the trial. 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 database.

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.

SAE [redacted]) Data Management

During the trial, data pertaining to SAEs reported on eSAE Forms will be integrated into the Sponsor's centralized GPV database.

Upon receipt of an eSAE Form, the data will be entered into the GPV database after a duplicate check. Each SAE case will be assigned a case identification number. Each case will be entered in the GPV database and assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. Assessment of related cases will be done in collaboration with the PSO 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 pertaining to SAEs in the GPV database will be reconciled with that in the clinical database.

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 safety data review will be performed by the Sponsor's SMT. For all periodic safety reviews, blinded safety data will provided to 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 statistical analysis plan (SAP) will be written and peer reviewed before any analyses. In accordance with the protocol, the SAP will describe all analyses to be performed under the responsibility of the Sponsor and all the conventions to be taken.

12.1.1 Hypotheses and Statistical Methods for Primary Objectives

Two co-primary objectives will be evaluated.

12.1.1.1 Primary Objective 1

Non-inferiority testing after 1 dose of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy

The percentages of subjects who achieve an hSBA titer ≥ 1:8 for meningococcal serogroups A, C, Y, and W in toddlers who received MenACYW conjugate vaccine (Group 1 and Group 3) are non-inferior to the corresponding percentages in toddlers who received Nimenrix® (Group 2 and Group 4) 30 days post administration.

Null hypothesis (H_0): $p_{(Men)} - p_{(Nim)} \leq -10\%$
Alternative hypothesis (H_1): $p_{(Men)} - p_{(Nim)} > -10\%$

where $p_{(Men)}$ and $p_{(Nim)}$ are the percentages of subjects who achieve an hSBA titer ≥ 1:8 in the MenACYW vaccine group and the Nimenrix® group, 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 percentages is > -10%, the inferiority assumption will be rejected.

For the 4 non-inferiority hypotheses using the response rates (percentages of subjects who achieve an hSBA titer ≥ 1:8), the 95% CI will be stratified on the priming status (meningococcal vaccine naïve or primed monovalent MenC vaccination during infancy) and calculated using the Wald method (normal approximation). Weighted average of the difference over strata will be calculated using the Minimal Risk weights with the null variance method (43).

The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

12.1.1.2 Primary Objective 2

Non-inferiority testing after 1 dose of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix®, the percentages of subjects who achieve an hSBA titer ≥ 1:8 for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$

Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA titer ≥ 1:8 in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages is > -10%, the inferiority assumption will be rejected.

For the 4 non-inferiority hypotheses using the response rates (percentages of subjects who achieve an hSBA titer ≥ 1:8), the CI of the difference in proportions will be computed using the Wilson

Score method without continuity correction (44). The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

To conclude, non-inferiority in toddlers who either are meningococcal vaccine-naïve or have received monovalent MenC vaccination during infancy and non-inferiority in meningococcal vaccine-naïve subjects have to be demonstrated.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

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

12.1.2.1 Secondary Objective 1

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy, the hSBA geometric mean titer ratio (GMTR) between MenACYW conjugate vaccine or Nimenrix® will be calculated, and 95% CI will be provided. The 95% CI of the ratio of post-vaccination GMTs will be stratified on the priming vaccination status (meningococcal vaccine naïve or primed monovalent MenC vaccination) and calculated using an analysis of variance (ANOVA) model of $\log_{10}$-transformed titers.

12.1.2.2 Secondary Objective 2

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers, the hSBA GMTR between MenACYW conjugate vaccine or Nimenrix® will be calculated, and 95% CI will be provided.

12.1.2.3 Secondary Objective 3

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccination during infancy, the hSBA GMTR between MenACYW conjugate vaccine or Nimenrix® will be calculated, and 95% CI will be provided

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 Nimenrix®. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages (45). For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Nimenrix® treatment groups.

In summary, descriptive analyses on A, C, Y, and W serogroups will include but not be limited to:

- hSBA GMT and 95% CI at D0 and D30
- hSBA titer distribution and RCDC
- Percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and 95% CI at D0 and D30
- Percentage of subjects with hSBA titer ≥4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- hSBA vaccine seroresponse[a] rate and 95% CI
- rSBA[b] GMT and 95% CI at D0 and D30
- rSBA[b] titer distribution and RCDC
- Percentage of subjects with rSBA[b] titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- rSBA[b] vaccine seroresponse[c] rate and 95% CI
- Percentage of subjects with rSBA[b] titers ≥ 1:8 and ≥ 1:128 and 95% CI at D0 and D30

Safety

For this trial, the safety data will be assessed by applying descriptive statistical methods, supplemented by the calculation of CIs to aid interpretation. The exact binomial distribution (Clopper-Pearson method) for proportions will be used in the calculation of the 95% CIs of events.

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

Unsolicited AEs will be collected, coded, and summarized by MedDRA system organ class and preferred term. For each unsolicited AE, the number of subjects with at least 1 instance of that event will be reported. Unsolicited AEs will also be tabulated by intensity and relatedness of study vaccine and by other categories specified by the endpoints.

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[a] hSBA vaccine seroresponse 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 that the pre-vaccination titer.

[b] In a subset of subjects per group: 100 subjects each in Group 1 and Group 2; 50 subjects in each subgroup (MenC-TT or MenC-CRM primed subjects) in Group 3; 25 subjects in each subgroup (MenC-TT or MenC-CRM primed subjects) in Group 4

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

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

12.2 Analysis Sets

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

12.2.1 Full Analysis Set

The FAS is defined as the subset of subjects who received at least 1 dose of the study vaccine and had a valid post-vaccination serology result. All subjects will be analyzed according to the treatment group to which they were randomized.

12.2.2 Safety Analysis Set

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. If the vaccine received by a subject does not correspond to any study group, the subject will be excluded from the SafAS. The corresponding safety data will be presented in separate listings.

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 post-dose serology sample in the proper time window or a post-dose serology sample was not drawn. The time windows are defined as D30 to D44 post-vaccination.
- Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine
- Subject's serology sample did not produce a valid test result
- Subject had other protocol deviations that affected the subject's immune response, as determined by the clinical team before locking the database

12.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

The safety analyses 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:

- Calculate the fold-rise of values as the ratio of post-baseline computed value divided by baseline computed value

If baseline or post baseline value is missing, then the seroconversion is missing.

12.3.3 Efficacy

Not applicable.

12.4 Interim/Preliminary Analysis

No interim or preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

[redacted]

[redacted]

13 Ethical and Legal Issues and Investigator/Sponsor Responsibilities

13.1 Ethical Conduct of the Trial/Good Clinical Practice

The conduct of this trial 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 trial source documents is to document the existence of subjects and to substantiate the integrity of the trial 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 DC, and transfer the information to the CRF.

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

The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any later 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.

13.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the trial, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur.

Sanofi Pasteur personnel (or designates), the IECs/IRBs, and regulatory agencies, including the Food and Drug Administration (FDA), require direct access to all study records, and will treat these documents in a confidential manner.

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.

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the trial (i.e., before the inclusion of the first subject in the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the trial protocol and the detailed trial procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRF 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 trial has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the trial, 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 Guidelines for entering data into the CRF, and the Operating Guidelines for detailed trial procedures such as the product management and sample-handling procedures.

After the start of the trial, 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 CRFs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the trial 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 CRFs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRF, 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 trial, 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 and Medical Quality Operations department (C&MQO) or by independent auditors to verify that the trial 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 trial documents during these inspections and audits.

13.4.3 Archiving

The Investigator must keep all trial documents after the completion or discontinuation of the trial, 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, trial documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any trial documents upon less than 90 days advance written notification to the Sponsor. In addition, trial 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 trial 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 trial, including certificates attesting that satisfactory audit and inspection procedures have been carried out, will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

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

13.6 Stipends for Participation

Subjects may be provided with a stipend according to local practice to compensate for the travel costs incurred for study visits and procedures.

13.7 Publication Policy

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

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

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

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