NCT03890367

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Versus Nimenrix® or NeisVac-C® in Healthy Toddlers 12 to 23 Months of Age

Phase III, modified double-blind, randomized, 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 licensed NeisVac-C® or Nimenrix® in toddlers in Europe.

Clinical Study Protocol, Amendment 1

Health Authority File Number(s):	EudraCT #: 2018-003790-10
WHO Universal Trial Number (UTN):	U1111-1217-2456
Study Code:	MEQ00065
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur 14 Espace Henry Vallée, 69007 Lyon, France
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) 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:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Coordinating Investigator:	This is a multi-center trial with multiple investigators; Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document
Sponsor's Responsible Medical Officer:	[redacted]

Local Medical Officer: [redacted]

Project Manager and Study Leader: [redacted]

Global Safety Officer:

Regional Trial Manager:

Version and Date of the Protocol: Version 4.0, dated 15 May 2020

History of Protocol Versions

Version	Date	Comments
1.0	20 December 2018	Internal version not submitted to the Health Authorities and the IEC/IRB
2.0	08 January 2019	Initial version submitted to the Health Authorities
3.0	15 March 2019	First approved version used in the study

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Synopsis

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

Title of the Study:	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Versus Nimenrix® and NeisVac-C® in Healthy Toddlers 12 to 23 Months of Age
Development Phase:	Phase III
Coordinating Investigator:	This is a multi-center trial with multiple investigators.
Study Sites:	This will be a multi-center, multi-country trial with approximately 31 trial centers in European countries. Investigators and sites will be listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	3Q 2019 –4Q 2020
Study Design, Schedule of Study Procedures, and Methodology:	This will be a Phase III, modified double-blind, randomized, parallel-groups, active-controlled, multi-center trial to compare the immunogenicity of a single dose of MenACYW conjugate vaccine to a single dose of a licensed quadrivalent meningococcal polysaccharide groups A, C, W-135, Y conjugate vaccine (MenACWY-TT, Nimenrix®) or of a licensed monovalent meningococcal group C conjugate vaccine (MenC-TT, NeisVac-C®) in toddlers, 12 to 23 months of age in Europe who are meningococcal vaccine naïve. <u>Vaccination</u> Approximately 705 healthy toddlers aged 12 to 23 months who have not received any meningococcal vaccine during infancy will be randomized in a 1:1:1 ratio to receive one dose of vaccine on Day (D) 0 (D0) at Visit 1 (V01) in one of the following 3 arms : • Group 1: MenACYW conjugate vaccine (n=235) • Group 2: Nimenrix® vaccine (MenACWY-TT conjugate vaccine) (n=235) • Group 3: NeisVac-C® vaccine (MenC-TT conjugate vaccine) (n=235) The randomization will be stratified by Center. <u>Blood sampling</u> All subjects will provide a pre-vaccination blood sample at V01 on D0 and a post-vaccination blood sample at Visit 2 (V02) (30 to 44 days after the vaccination at V01), for immunogenicity assessment. <u>Collection of safety data</u> - All subjects will be followed for safety from V01 on D0 to V02 after vaccination. - All subjects will be observed for 30 minutes after vaccination and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited AEs in the electronic case report book (eCRB). - The subject's parent or another legally acceptable representative will record information in a diary card about solicited reactions from D0 to D7 after vaccination and unsolicited AEs will be recorded from D0 to D30.

	- Serious adverse events (SAEs, including adverse events of special interest [AESIs]) will be recorded in a diary card throughout the study. The subject's parent / legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the study. - Study site staff will contact subjects' parent / legally acceptable representative by telephone on 8 days (+ 2 days) after V01 to identify the occurrence of any SAEs (including AESIs) not yet reported and to remind them to complete the diary card and bring it back to V02. - The completed diary card will be collected and reviewed with the subject's parent / legally acceptable representative at V02.
Interruption of the Study:	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs (Independent Ethics Committees)/IRBs (Institutional Review Boards), or the governing regulatory authorities in the countries where the study is taking place. There will be an internal team at the level of the Sponsor (Safety Management Team [SMT]), which will review the data being generated from all ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in recruitment while it investigates any potential signal or concern. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subjects' parents/legally acceptable representatives and should assure appropriate subject therapy and/or follow-up.
Primary Objectives:	1) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by serum bactericidal assay using human complement (hSBA). If the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) is demonstrated, then 1.1) To demonstrate the non-inferiority of the antibody response (geometric mean titers [GMT]) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then 1.2) To demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. If the superiority of the antibody response (GMT) is demonstrated, then 1.3) To demonstrate the superiority of the seroprotection rate to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. 2) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by serum bactericidal assay using baby rabbit complement (rSBA). If the non-inferiority of the seroprotection rate is demonstrated, then 2.1) To demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by rSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then

	2.2) To demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by rSBA. Overall, the primary objective for the study will be met if, objective 1) - non-inferiority of the seroprotection rate versus Nimenrix® as measured by hSBA, or objective 2) - non-inferiority of the seroprotection rate versus NeisVac-C® as measured by rSBA, is met.
Primary Endpoints:	1) Antibody titers against meningococcal serogroup C measured by hSBA, 30 days (+ 14 days) after vaccination: • ≥ 1:8, with MenACYW conjugate vaccine or Nimenrix® • With MenACYW conjugate vaccine or Nimenrix® 2) Antibody titers against meningococcal serogroup C measured by rSBA, 30 days (+ 14 days) after vaccination: • ≥ 1:8, with MenACYW conjugate vaccine or NeisVac-C® • With MenACYW conjugate vaccine or NeisVac-C®
Secondary Objectives:	1) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA. If the non-inferiority of the seroprotection rate is demonstrated, then 1.1) To demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then 1.2) To demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA 2) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA. If the non-inferiority of the seroprotection rate is demonstrated, then 2.1) To demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then 2.2) To demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA Overall, the secondary objective for the study will be met if objective 1) - non-inferiority of the seroprotection rate versus Nimenrix® as measured by rSBA, or objective 2) - non-inferiority of the seroprotection rate versus NeisVac-C® as measured by hSBA, is met.
Secondary Endpoints:	1) Antibody titers against meningococcal serogroup C measured by rSBA,30 days (+ 14 days) after vaccination: • ≥ 1:8, with MenACYW conjugate vaccine or Nimenrix® • With MenACYW conjugate vaccine or Nimenrix® 2) Antibody titers against meningococcal serogroup C measured by hSBA, 30 days (+ 14 days) after vaccination: • ≥ 1:8 with MenACYW conjugate vaccine or NeisVac-C® • With MenACYW conjugate vaccine or NeisVac-C®

Observational Objectives:	***Immunogenicity*** 1) To describe the antibody response to meningococcal serogroup C before and 30 days (+ 14 days) after vaccination in each group using hSBA in toddlers 2) To describe the antibody response to meningococcal serogroup C before and 30 days (+ 14 days) after vaccination in each group using rSBA in toddlers ***Safety*** To describe the safety profile of MenACYW conjugate vaccine, Nimenrix® and NeisVac-C®.
Observational Endpoints:	***Immunogenicity*** *Observational Objective 1:* • Antibody titer against meningococcal serogroup C measured by hSBA in each group: • Assessed before and at 30 days (+ 14 days) after vaccination • ≥ 1:4 and ≥ 1:8, assessed at 30 days (+ 14 days) after vaccination • ≥ 4-fold rise from pre-vaccination to post-vaccination • Post-vaccination / pre-vaccination titer ratio • Vaccine seroresponse measured by hSBA* in each group with seroresponse defined as: - For a subject with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16 - For a subject with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer. *Observational Objective 2*: • Antibody titers against meningococcal serogroup C measured by rSBA in each group: • Assessed before and at 30 days (+ 14 days) after vaccination • ≥ 1:8 and ≥ 1:128, assessed before and at 30 days (+ 14 days) after vaccination • Post-vaccination / pre-vaccination titers ratio • ≥ 4-fold rise from pre-vaccination to post-vaccination • Vaccine seroresponse measured by rSBA, with seroresponse defined as: - For a subject with pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32 - For subjects with pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer ***Safety*** The safety profile of the 3 vaccines will be evaluated within 30 days (+ 14 days) after the vaccination. The following endpoints will be used for all subjects for the evaluation of safety: • Unsolicited systemic AEs reported in the 30 minutes following the vaccination • Solicited (pre-listed in the subject diary and the electronic Case Report Form [CRF]) injection site reactions and systemic reactions starting anytime from D0 (Day of vaccination) through D7 after the vaccination • Unsolicited (spontaneously reported) non-serious AEs up to from D0 and D30 • SAEs (including AESIs) throughout the study, ie, from D0 to Visit 2 Depending on the items, the endpoints recorded or derived could include: Nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration / number of days of occurrence, intensity, relationship to vaccine, whether the AE led to early termination from the study, seriousness criterion, outcome.

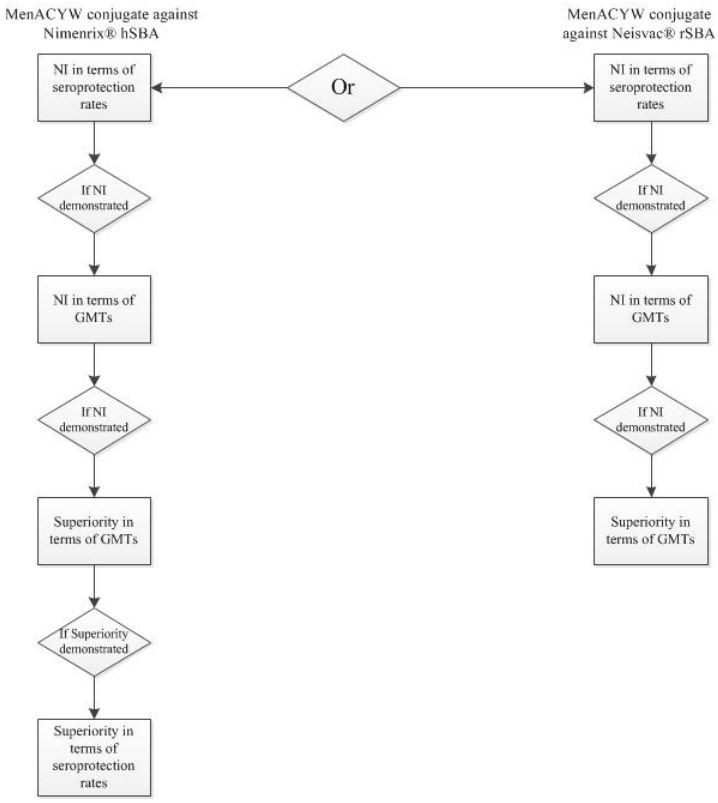
Planned Sample Size:	A total of 675 subjects were initially planned to be enrolled (with an estimated drop-out rate of 10%). • Group 1: MenACYW conjugate vaccine ..... n=225 to be enrolled (202 evaluable) • Group 2: Nimenrix® vaccine ..... n=225 to be enrolled (202 evaluable) • Group 3: NeisVac-C® vaccine ..... n=225 to be enrolled (202 evaluable) As a consequence of the COVID-19 pandemic, enrollment was paused on17 March 2020. Approximately 30 subjects were identified to be excluded from the per-protocol analysis set (PPAS) due to COVID-19 as they were unable to complete their follow-up visit as planned per the protocol. The sample size of the study will then be modified to replace these subjects. Approximately 705 subjects will now be enrolled (235 in each group). In the event of any new unexpected situations impacting study visits, the sample size might be increased to replace subjects excluded from the PPAS.
Duration of Participation in the Study:	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, W, and Y) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Form:	Liquid solution 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 micrograms (µg) Serogroup C ..... 10 µg Serogroup Y ..... 10 µg Serogroup W ..... 10 µg Tetanus toxoid protein carrier ..... approximately 55 µg* * Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation.
Route:	Intramuscular (IM)
Batch #	To be determined
Control Product:	Nimenrix®: Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)
Form:	Lyophilized powder in a vial and diluent for reconstitution in a pre-filled syringe
Composition:	Each 0.5 mL dose of Nimenrix® vaccine 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 .....approximately 44 µg Excipients: In the powder: Sucrose, Trometamol In the solvent: Sodium chloride, Water for injections
Route:	IM
Batch #	Commercial lot to be supplied by Sponsor

Control Product:	NeisVac-C®: Meningococcal Group C Polysaccharide Conjugate Vaccine Adsorbed (Pfizer Limited, Sandwich, United Kingdom)
Form:	Suspension for injection in pre-filled syringe
Composition:	Each 0.5 mL dose of NeisVac-C® vaccine is formulated to contain: *Neisseria meningitidis* serogroup C (strain C11) polysaccharide (de-O-acetylated).....10 µg conjugated to tetanus toxoid.....10-20 µg adsorbed on aluminium hydroxide, hydrated .....0.5 mg Al3+ Excipients: Sodium chloride, Water for injections
Route:	IM
Batch #	Commercial lot to be supplied by Sponsor
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for study enrollment: 1) Aged 12 to 23 months on the day of the first study visit 2) Informed consent form (ICF) has been signed and dated by the parent(s) / legally acceptable representative(s) 3) Subject and parent / legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures 4) Covered by health insurance if required by local regulations
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) Participation in the 4 weeks (28 days) preceding the study vaccination or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure 2) Receipt of any vaccine in the 4 weeks (28 days) preceding the study 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) Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B vaccine) 5) 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) 6) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically 7) At high risk for meningococcal infection during the study (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease) 8) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances 9) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine

	10) Personal history of Guillain-Barré syndrome (GBS) 11) Thrombocytopenia, as reported by the parent/ legally acceptable representative or suspected thrombocytopenia contraindicating intramuscular vaccination in the Investigator's opinion 12) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion 13) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion 14) 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. 15) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 16) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study
Statistical Methods:	**Primary Objective** The immunogenicity of MenACYW conjugate vaccine serogroup C will be compared to that of Nimenrix® vaccine and to that of NeisVac-C® vaccine using sequential testing approaches. ***Non-Inferiority*** A non-inferiority testing approach will be used to compare post-vaccination (ie, 30 days after the vaccination) seroprotection rates and GMTs of MenACYW conjugate vaccine to that of Nimenrix® and NeisVac-C®, using a two-sided 95% Confidence Interval (CI) with the following hypotheses: For seroprotection rates: $H_0 : \pi_{\text{MenACYW}} - \pi_{Comparator} \leq -0.1$ $H_1 : \pi_{\text{MenACYW}} - \pi_{Comparator} > -0.1$ Or For GMTs $H_0 : GMT_{\text{MenACYW}} / GMT_{Comparator} \leq 1/\delta$ $H_1 : GMT_{\text{MenACYW}} / GMT_{Comparator} > 1/\delta$ with: • Comparator: Nimenrix® or NeisVac-C® • π: seroprotection rates • δ: non-inferiority margin set at 1.5 ***Superiority*** If the non-inferiority testing succeeds then a superiority approach will be used to compare post-vaccination (ie, 30 days after the vaccination) seroprotection rates and/or GMTs of MenACYW conjugate vaccine to that of Nimenrix® and NeisVac-C®, using a two-sided 95% CI with the following hypotheses:

	For seroprotection rates $$H_0 : \pi_{\text{MenACYW}} - \pi_{Comparator} \leq 0$$ $$H_1 : \pi_{\text{MenACYW}} - \pi_{Comparator} > 0$$ Or For GMTs $$H_0 : GMT_{\text{MenACYW}} / GMT_{Comparator} \leq 1$$ $$H_1 : GMT_{\text{MenACYW}} / GMT_{Comparator} > 1$$ with: • Comparator: Nimenrix® or NeisVac-C® • π: seroprotection rates For the seroprotection rates, the 95% CI of the difference in proportions will be computed using the Wilson Score method without continuity correction (Newcombe method). For the GMTs, the two-sided 95% CI of the ratio of post-vaccination GMTs will be calculated using normal approximation of log-transformed titers. The non-inferiority will be demonstrated against seroprotection rates if the null hypothesis is rejected, ie, if the lower limit of the two-sided 95% CI for the difference between the seroprotection rates is > -10%. The non-inferiority will be demonstrated against GMTs if the null hypothesis is rejected, ie, lower limit of the two-sided 95% CI for the ratio of GMTs > 1/1.5. The superiority will be demonstrated against seroprotection rates if the null hypothesis is rejected, ie, if the lower limit of the two-sided 95% CI for the difference between the seroprotection rates is > 0%. The superiority will be demonstrated against GMTs if the null hypothesis is rejected, ie, lower limit of the two-sided 95% CI for the ratio of GMTs > 1. The testing approach will be done in parallel and using a step by step approach for the 2 comparators: *Nimenrix®*: If the non-inferiority using seroprotection rates of MenACYW conjugate vaccine against Nimenrix® measured by hSBA is demonstrated then the non-inferiority using hSBA GMTs will be tested. If the non-inferiority using hSBA GMTs of MenACYW conjugate vaccine against Nimenrix® is demonstrated then the superiority using hSBA GMTs will be tested. If the superiority using hSBA GMTs is demonstrated then the superiority using hSBA seroprotection rates will be tested. *NeisVac-C®*: If the non-inferiority using seroprotection rates of MenACYW conjugate vaccine against NeisVac-C® measured by rSBA is demonstrated then the non-inferiority using rSBA GMTs will be tested. If the non-inferiority using rSBA GMTs is demonstrated then the superiority using rSBA GMTs will be tested.

Figure 1: Sequential statistical testing approach for primary objectives



To conclude, non-inferiority using seroprotection rates of MenACYW conjugate vaccine against Nimenrix® measured by hSBA or non-inferiority using seroprotection rates of MenACYW conjugate vaccine against NeisVac-C® measured by rSBA have to be demonstrated.

Secondary Objectives

A similar statistical approach as for the primary objective will be used considering the rSBA antibody titers for Nimenrix® and hSBA antibody titers for NeisVac-C®.

The testing approach will be done in parallel and using a step by step approach for the 2 comparators:

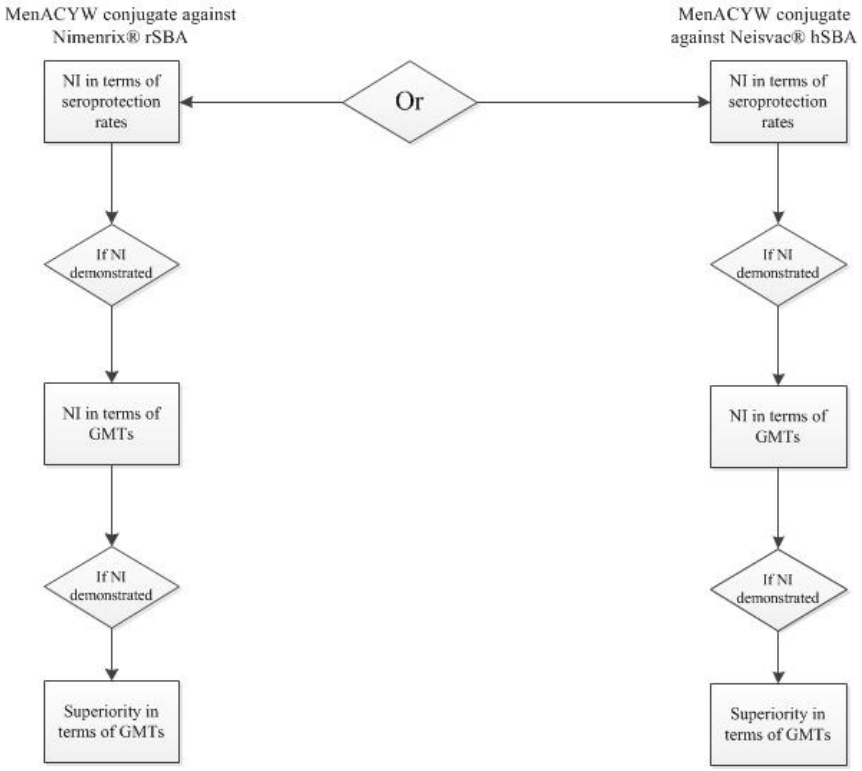
Nimenrix®:

If the non-inferiority using seroprotection rates of MenACYW conjugate vaccine against Nimenrix® measured by rSBA is demonstrated then the non-inferiority using rSBA GMTs will be tested. If the non-inferiority using rSBA GMTs of MenACYW conjugate vaccine against Nimenrix® is demonstrated then the superiority using rSBA GMTs will be tested.

NeisVac-C®:

If the non-inferiority using seroprotection rates of MenACYW conjugate vaccine against NeisVac-C® measured by hSBA is demonstrated then the non-inferiority using hSBA GMTs will be tested. And if the non-inferiority using hSBA GMTs is demonstrated then the superiority using hSBA GMTs will be tested.

Figure 2: Sequential statistical testing approach for secondary objectives



To conclude, non-inferiority using seroprotection rates of MenACYW conjugate vaccine against Nimenrix® measured by rSBA or non-inferiority using seroprotection rates of MenACYW conjugate vaccine against NeisVac-C® measured by hSBA have to be demonstrated.

Observational Objectives

For immunogenicity and safety observational objectives, the descriptive analyses will be done according to each vaccine group. The main parameters will be described with 95% CI using the exact binomial distribution (Clopper-Pearson method) for proportions and using the normal approximation of the Log_{10} concentrations/titers, followed by a back transformation for GMTs.

Calculation of Sample Size:

To complete the primary objective a total of 675 subjects were initially planned to be enrolled according to a ratio 1:1:1 (MenACYW: Nimenrix®: NeisVac-C®). This sample size will provide acceptable global powers considering an overall one-sided alpha of 2.5% (ie, 1.25% adjusted alpha for each of the 2 main non-inferiority tested, then same level of alpha is used for the subsequent tests as a ranking testing strategy is used), an initial drop-out rate of 10% (ie, 202 evaluable subjects per group; not taking into account the impact of COVID-19) and based on the following additional hypotheses:

Statistical hypotheses and powers for the primary objective

Objective number	Step	Comparator	Statistical test	Endpoint	Ref. MenACYW vs Comparator	Clinical margin	Standard deviation (SD)	Indivi-dual power	Sequential power
1	1	Nimenrix hSBA	NI	Seroprotection rates	98% vs 88%	10%		>99.9%	>99.9%
	2	Nimenrix hSBA	NI	GMTs	GMTR=1.5	1.5	0.5	>99.9%	>99.9%
	3	Nimenrix hSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	89.9%
	4	Nimenrix hSBA	Sup	Seroprotection rates	98% vs 88%	10%		95.8%	86.1%
2	1	Neisvac-C rSBA	NI	Seroprotection rates	98% vs 98%	10%		>99.9%	>99.9%
	2	Neisvac-C rSBA	NI	GMTs	GMTR=1	1.5	0.5	90.1%	90.1%
	3	Neisvac-C rSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	81.2%

NI: non-inferiority; Sup: superiority
GMTR: Geometric Mean of Titers ratios of MenACYW vs Comparator
One-sided Alpha of 1.25% used for all calculations
Sequential power correspond to the overall power of each step of the statistical tests to be performed
Reference seroresponse rates and SDs made from Phase II and III toddler studies MET51, MET32 and MET54.

In addition, considering such sample size will also provide acceptable global powers to achieve the secondary objective, considering an overall one-sided alpha of 2.5% (ie, 1.25% adjusted alpha for each of the 2 main non-inferiority tested, then same level of alpha is used for the subsequent tests as a ranking testing strategy is used), an initial drop-out rate of 10% (not taking into account the impact of COVID-19), and based on the following additional hypotheses:

Statistical hypotheses for the secondary objective

Objective number	Step	Comparator	Statistical test	Endpoint	Ref. MenACYW vs Comparator	Clinical margin	Standard deviation (SD)	Indivi-dual power	Sequential power
1	1	Nimenrix rSBA	NI	Seroprotection rates	98% vs 98%	10%		>99.9%	>99.9%
	2	Nimenrix rSBA	NI	GMTs	GMTR=1.5	1.5	0.5	>99.9%	>99.9%
	3	Nimenrix rSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	90.1%
2	1	Neisvac-C hSBA	NI	Seroprotection rates	98% vs 98%	10%		>99.9%	>99.9%
	2	Neisvac-C hSBA	NI	GMTs	GMTR=1	1.5	0.5	90.1%	90.1%
	3	Neisvac-C hSBA	Sup	GMTs	GMTR=1.5	-	0.5	90.1%	81.2%

NI: non-inferiority; Sup: superiority
GMTR: Geometric Mean of Titers ratios of MenACYW vs Comparator
One-sided Alpha of 1.25% used for all calculations
Sequential power correspond to the sequential power of each step of the statistical tests to be performed
Reference seroresponse rates and SDs made from Phase II and III toddler studies MET51, MET32 and MET54.

As a consequence of the COVID-19 hold, approximately 30 subjects were identified to be excluded from the PPAS as they were unable to complete their follow-up visit as planned in the protocol. To maintain the planned study power and the randomization ratio, approximately 30 additional subjects are planned to be enrolled, with a planned final distribution of 235:235:235.

Table of Study Procedures

Phase III Trial, 2 Visits, 1 Phone Call, 1 Vaccination, 2 Blood Samples, 30 to 44 Days' Duration per Subject

Visit/Contact	Visit 1	Telephone Call 1	Visit 2
Trial timelines (days)	D0	D8	D30
Time windows (days)	-	+2 days	+14 days
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Medical history	X		
Physical examination and Temperature	X		
Contact Interactive Response Technology (IRT) for randomization	X		
Review of temporary contraindications for blood sampling*			X
Blood sample (BL), 4 mL†	BL0001		BL0002
Vaccination‡	X		
Immediate surveillance (30 minutes)	X		
Diary card provided	X		
Telephone call		X§	
Recording of solicited injection site & systemic reactions	D0 to D7		
Recording of unsolicited AEs	D0 to D30		
Reporting of SAEs (including AESIs)	To be reported throughout the study period		
Diary card reviewed and collected			X
Collection of reportable concomitant medications	To be reported throughout the study period		
Termination record			X

* 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), when possible.

† Blood sample at Visit 1 will be drawn before administration of the vaccine.

‡ Subjects will receive 1 dose of MenACYW conjugate vaccine or Nimenrix® or NeisVac-C®.

§ This call is made 8 to 10 days after the vaccination at Visit 1. If D8 (+ 2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE (including AESIs) not yet reported, and will remind the subject's parent / legally acceptable representative to continue using the diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2.

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CDM	Clinical Data Management
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CSU	Sanofi Clinical Study Units
CTA	clinical trial agreement
CTL	Clinical Team Leader
DC	diary card
EDC	electronic data capture
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 titers
GPV	Global Pharmacovigilance
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonization

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMD	invasive meningococcal disease
IME	important medical event
IND	investigational new drug (application)
IOM	Institute of Medicine
IRB	Institutional Review Board
IRT	interactive response technology
LCLS	last contact, last subject
LLOQ	lower limit of quantification
LLT	lowest level term
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MenC	Meningococcal C
mL	Milliliter
MTL	Medical Team Leader
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
PMSL	Project Manager and Study Leader
RME	Regional Medical Expert
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SAP	statistical analysis plan
SafAS	safety analysis set
SD	standard deviation
SMT	Safety Management Team
SP	Sanofi Pasteur
TC	telephone call
TMF	trial master file
TT	tetanus toxoid
ULOQ	upper limit of quantification
US	United States
WHO	World Health Organization

1 Introduction

1.1 Background

This is a study using the quadrivalent meningococcal polysaccharide (serogroups A, C, Y and W) tetanus toxoid conjugate vaccine (hereafter referred to as MenACYW conjugate vaccine) against invasive meningococcal disease (IMD) in healthy toddlers 12 to 23 months of age who are meningococcal vaccine naïve.

The purpose of this study (MEQ00065) is to compare the immunogenicity of Serogroup C of a single dose of MenACYW conjugate vaccine to a single dose of licensed vaccines, NeisVac-C® (Meningococcal C–TT conjugate vaccine) or Nimenrix® (quadrivalent Meningococcal ACWY-TT conjugate vaccine) and to describe the safety in healthy toddlers 12 to 23 months of age who are meningococcal vaccine naïve in Europe. The purpose of this study is to demonstrate that the immunogenicity of MenACYW conjugate vaccine is at least non-inferior to that of Nimenrix® (MenACWY-TT conjugate vaccine), and NeisVac-C® (meningococcal C [MenC]-TT conjugate vaccine), for serogroup C.

IMD is a serious illness caused by the bacterium *Neisseria meningitidis (N. meningitidis)*, a Gram-negative diplococcus found exclusively in humans. It is associated with high morbidity and mortality. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial or purpuric rash (1). Invasive infection usually results in septicemia (~35%–40% of cases), meningitis (~50% of cases), or both. Bacteremic pneumonia is less common (~9% of cases) (2). At least 12 different 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, 3, 4). Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (3-5). Serogroup B is responsible for endemic disease and some outbreaks, while serogroup C is responsible for large outbreaks (6). Serogroup A remains the main cause of epidemics in the world and is especially dominant in Africa and Asia but is only minor in Europe. Serogroup W has been observed in Africa, as well as in the United Kingdom (UK), in residents who participated in the Hajj pilgrimage to the Kingdom of Saudi Arabia (5, 7, 8) and in other parts of the world. An increasing trend of the notification rate of W serogroup is seen in Europe (9). Serogroup X causes substantial meningococcal disease in parts of Africa, but rarely causes disease in other parts of the world (3, 10). Serogroup Y has not been associated with outbreaks, but the frequency with which it causes sporadic cases has gradually increased in the United States (US) and more recently in Canada and Europe (11-13). The Y serogroup is commonly associated with meningococcal pneumonia, particularly in older adults ≥ 65 years of age (14).

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 European Center for Disease Prevention and Control (ECDC) publish annually an epidemiological report on Invasive Meningococcal Disease, based on data retrieved from the European Surveillance System (TESSy) which is used to collect, analyze and disseminate data on communicable diseases. Thirty EU/EEA Member states contribute to the system by uploading

regularly their infectious disease surveillance data. The last report has been published in August 2018, based on 2016 data (9). In 2016, the overall incidence rate of IMD in European Union (EU)/European Economic Area (EEA) countries was 0.6 per 100 000 similar to the notification rate for previous years. Four countries (France, Germany, Spain and the United Kingdom) accounted for 60% of all confirmed cases. The incidence per 100 000 was of 0.3 in Finland, 0.7 in Denmark and 0.4 in Germany. In 2016, IMD notification rate was 2.7 confirmed cases per 100 000 population in 1-4-year-olds (1). IMD was predominantly notified in infants and young children with a notification rate of 8.5 confirmed cases per 100 000 population in children under one year of age and 2.7 confirmed cases per 100 000 population in 1-4-years-old. Infants were the most affected age group in the majority of Member States.

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 (9). By 2016, meningococcal C conjugate (MCC) vaccine was integrated into the national routine childhood immunization programs of 14 EU/EEA countries. In countries without national routine MCC vaccination, serogroup C accounted for 21% of cases. In countries with national routine MCC vaccination, 15% of cases were attributed to serogroup C.

The trend in serogroup C was stable at the EU level. Although the trend in serogroup Y was stable at the EU level during the time period presented in this report, several EU/EEA countries have reported increasing trends in serogroup Y in recent years. Serogroup W has increased at the European level since 2011, predominantly due to the rapid epidemic expansion of a single clone in the UK that started in 2009, but other EU Member States also experienced an increase in serogroup W.

The incidence of IMD due to serogroup C is declining in Germany, the incidence of IMD due to serogroup W and Y are increasing. The numbers of IMD cases due to these three serogroups are now very similar. For instance, in 2017, the number of cases reported for serogroup C, W and Y were 39, 21 and 35, respectively, although in 2014, they were 41, 10 and 19, respectively. In 2017, most MenB cases were reported in infants aged below 1 year with an increase again at 15 years. MenC was more common in adolescents and young adults aged between 15 and 20 years. MenW and MenY were more common in the 15–24 years group and over 50 years group. There was only one case of MenA, observed in a 3-year-old. The upward trend since 2014 in MenW and MenY cases has been especially clear in the adolescent and young adult population (15–24 years) with a spike in MenY incidences in 2016.

Over the last ten years Denmark had shown a similar picture as described above for Germany (15).

In this context of increasing trends for serogroups W and Y, Austria, the Czech Republic, Greece, Italy and the UK have introduced the quadrivalent conjugate vaccine MenACYW into their routine vaccination schedules, predominantly as booster doses for adolescents. As carriage rates of Neisseria meningitidis are highest in adolescents and young adults, high coverage rate and levels of immunity in this age group are critical to ensure the protection of other vulnerable age groups. That is the reason why in 2018, the Netherlands have introduced also MenACWY vaccination targeting both toddlers (14 months of age) and adolescents (14 years of age). Some

Italian regions have also the same strategy with a switch from MenC to MenACWY vaccination in toddlers aged 14 months and MenACWY vaccination in adolescents.

MenACYW conjugate vaccine will provide broad protection against IMD caused by serogroups A, C, W, and Y in all age groups including 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

1.2.1 Clinical

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

The final formulation has been evaluated in over 7000 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in completed phase II and phase III studies MET35, MET39, MET43, MET44, MET49, MET50, MET51, MET54 and MET56. MenACYW conjugate vaccine is also being evaluated in ongoing Phase III studies: MET57 (in toddlers 12 to 23 months of age), MET58 (in infants and toddlers 6 weeks to 18 months of age), MET41 (in infants and toddlers 6 weeks to 15 months of age), MET42 (in infants and toddlers 6 weeks to 15 months of age), MET52 (in infants and toddlers 3 to 13 months of age), MET33 (in infants and toddlers from 6 weeks to 15 months of age) MET61 (in infants and toddlers 6 months to 23 months of age), and MET62 (in children 4 to 5 years of age).

Approximately 1500 toddlers (12 to 23 months of age) have received one dose of MenACYW conjugate vaccine in studies MET54, MET51, and MET57.

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. The relevant Phase II and Phase III studies are discussed below.

1.2.1.1 Study MET54 (Phase II)

MET54 was a Phase II, randomized, open-label, active-controlled, multi-center study conducted in Europe (Finland). This study evaluated the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine when given alone in healthy, meningococcal vaccine naïve toddlers compared to that of the licensed vaccine Nimenrix®. A total of 188 meningococcal vaccine naïve subjects aged 12 to 23 months on the day of enrollment were randomized to 1 of 2 groups. Group 1 received a single dose of MenACYW conjugate vaccine and Group 2 received a single dose of Nimenrix®.

Immunogenicity

Antibody responses to the antigens (serogroups A, C, W, and Y) were evaluated by serum bactericidal assay using baby rabbit complement (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.

hSBA

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

rSBA

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

Safety

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

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

No new clinically important safety findings were identified with administration of the MenACYW conjugate vaccine. The MenACYW conjugate vaccine was well tolerated and immunogenic. Single dose of the MenACYW conjugate vaccine demonstrated excellent potential to be an alternative vaccine option for toddlers, receiving meningococcal vaccination for the first time.

1.2.1.2 Study MET51 (Phase III)

This study focused on evaluating the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine compared to that of the licensed quadrivalent meningococcal serogroups A, C, W, and Y tetanus toxoid conjugate vaccine (MenACWY-TT, Nimenrix®) in toddlers in the European Union who were either meningococcal vaccine naïve or received MenC vaccination during infancy.

A total of 918 subjects were randomized to the following groups:

Meningococcal Vaccine-Naïve Subjects were randomized to the following 2 groups:

Group 1: MenACYW conjugate vaccine

Group 2: Nimenrix®

MenC-Primed Subjects: were randomized to the following 2 groups:

Group 3: MenACYW conjugate vaccine

Group 4: Nimenrix®

Immunogenicity

Non-Inferiority of MenACYW Conjugate Vaccine to Nimenrix® who were either meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy

Thirty days after vaccination, the lower limit of the 2-sided 95% CI of the overall stratified difference in hSBA response rates (antibody titers ≥ 1:8) between MenACYW Conjugate vaccine and Nimenrix® recipients were > -10% for all 4 serogroups. Non inferiority of immune response, based on percentage of subjects achieving a post vaccination titer ≥ 1:8 at D30 regardless of their meningococcal vaccine background, was demonstrated for MenACYW conjugate vaccine versus Nimenrix® for all serogroups.

Non-Inferiority of MenACYW Conjugate Vaccine to Nimenrix® who were meningococcal vaccine naïve

Thirty days after vaccination, the lower limit of the 2-sided 95% CI of the difference in hSBA response rates (antibody titers ≥ 1:8) MenACYW Conjugate Vaccine (Group 1) and Nimenrix® recipients (Group 2) were > -10% for all 4 serogroups. Non inferiority of immune response, based on percentage of subjects achieving a post vaccination titer ≥ 1:8 at D30 in meningococcal vaccine-naïve toddlers, was demonstrated for MenACYW conjugate vaccine versus Nimenrix® for all serogroups.

hSBA Vaccine Seroresponse at D30

At D30, the percentages of subjects with an hSBA vaccine seroresponse were higher in MenACYW-recipients than in Nimenrix®-recipients for serogroup C. For the other serogroups, percentages were similar between MenACYW-recipients and Nimenrix®-recipients.

Antibody Responses (hSBA GMTs) at D30

Toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy

The GMTRs (stratified on priming vaccination background) were 7.59, 1.28, and 1.32 for serogroups C, Y and W, respectively, with the lower bound of the 95% CI greater than 1.0; and the GMTR (stratified on priming vaccination background) was 0.819 for serogroup A, with the upper bound of the 95% CI lower than 1.0.

Meningococcal vaccine-naïve toddlers

The GMTRs were 1.03 and 1.18 (with the lower bound of the 95% CI below 1.0) for serogroups A and Y, respectively, and 16.5 and 1.34 (with the lower bound of the 95% CI greater than 1.0) for serogroups C and W, respectively.

Toddlers who received monovalent MenC vaccination during infancy

The GMTRs were 0.496 (with the upper bound of the 95% CI lower than 1.0) for serogroup A, 1.34 and 1.29 (with the lower bound of the 95% CI below 1.0) for serogroups C and W, respectively, and 1.53 (with the lower bound of the 95% CI greater than 1.0) for serogroup Y.

Antibody Responses (rSBA GMTs and seroresponse Titers ≥1:8 seroresponse) at D30

Toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy

At D30, meningococcal rSBA GMTs were lower in MenACYW-recipients than in Nimenrix®-recipients for serogroup A (1382 and 4882, respectively), and higher in MenACYW-recipients than in Nimenrix®-recipients for serogroup C (2150 and 686, respectively).

Thirty days after vaccination, the percentages of subjects with rSBA antibody titers ≥ 1:8 were high and comparable between MenACYW- and Nimenrix®-recipients ranging from 97.3% to 100.0%.

Safety

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

There was only 1 solicited injection site reaction reported larger than 100 mm. The subject, randomized in Group 1 (MenACYW–naïve), reported injection site erythema at 30 mm on D0 that lasted for 4 days. No action was taken. The majority of the solicited injection sites were of Grade 1 or 2 intensity, most started between D0 and D03, and most lasted 1 to 3 days. Overall, most solicited systemic reactions were of Grade 1 or Grade 2 intensity, started between D0 and D30, and lasted 1 to 3 days.

Seven subjects experienced a total of 11 SAEs during the study. None of these SAEs were considered as related to the investigational vaccine by the Investigator, and none led to discontinuation from the study. The percentages of subjects who reported at least 1 SAE during the study were less than 1% and comparable between MenACYW- and Nimenrix®-recipients. No deaths were reported during the study.

Vaccination with MenACYW conjugate vaccine among toddlers aged 12 to 23 months was found to be well tolerated, with no safety concerns identified.

1.2.1.3 Study MET57 (Phase III)

MET57, a Phase III study in 1200 toddlers aged 12 to 23 months, is currently ongoing in South Korea, Russia, Mexico, and Thailand. The study is designed to evaluate the safety and immunogenicity profile of the MenACYW conjugate vaccine when administered alone or concomitantly with routine pediatric vaccines for the age group being evaluated in the study

(Measles, Mumps, Rubella (MMR) and varicella in South Korea and Thailand; pneumococcal 13-valent conjugate (PCV13) vaccine in Russia; and DTaP, HB, IPV, and Hib conjugate combination vaccine in Mexico).

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

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

Subjects who receive NeisVac-C® will likely be protected against meningococcal disease caused by *N. meningitidis* serogroup C.

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

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

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine, NeisVac-C® 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 when administered to infants / toddlers. There may be a rare possibility of an allergic reaction, which could be severe. There may also be a risk of febrile convulsion in some children who experience high fever. There may be other risks for MenACYW conjugate vaccine, NeisVac-C® or Nimenrix® that are not yet known.

In a previous study with MenACYW conjugate vaccine (MET32), 1 SAE of reactive arthritis reported in a toddler was considered by the Investigator to be related to the investigational vaccine. The subject developed right knee inflammation the day after receiving MenACYW conjugate vaccine, given by IM injection in the right deltoid. The subject recovered after treatment with ibuprofen and antibiotics. Results of the reactive arthritis investigations performed as part of the workup were not indicative of any specific diagnosis. A point of further consideration was the monoarticular nature of the inflammation in this subject; reactive arthritis would typically be present clinically in a polyarticular fashion. Importantly, no similar cases have been reported following the administration of MenACYW conjugate vaccine in any other completed trials.

Guillain-Barré syndrome (GBS) has been reported in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of a US licensed meningococcal conjugate

vaccine (16). 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 (17).

A review by the Institute of Medicine (IOM) found inadequate evidence to accept or reject a causal relationship between tetanus toxoid-containing vaccines and GBS (18). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (19). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (20).

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 risk listed here are not exhaustive. Refer to the Investigator's Brochure (IB) of the investigational vaccine and to the Summary of Product Characteristics for NeisVac-C® (21) and Nimenrix® (22) for additional information regarding potential risks.

1.3.3 COVID-19 Risk Assessment

MenACYW conjugate vaccine, NeisVac-C®, and Nimenrix® would not cause immune suppression. Therefore, the risk that a participant in this study will contract COVID-19 solely due to the administration of the study vaccine will be similar to the risk that a person not participating in this study will contract COVID-19. However, the risk of exposure to infected people cannot be completely excluded as subjects may need to be exposed to public areas (eg, commute to the site and at the site).

Risk mitigation:

- Do not restart the study until local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by local Authorities.
- Continued risk assessment by the Investigator and Sponsor before deciding to restart the trial.
- Reduce public exposure while ambulatory when possible.

1.4 Rationale for the Study

Vaccination is currently the best option to prevent IMD. A number of vaccines are, either targeting single serogroup (such as serogroup C vaccines) or a combination or multiserogroups (quadrivalent vaccines) which provide broad coverage and have the potential to protect individuals in countries with several predominant circulating serogroups (as currently observed in Europe with C serogroups and increasing W and Y serogroups).

Two meningococcal C (MenC) conjugate vaccines are currently licensed in European countries from 2 months of age. 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) (Menjugate®) or tetanus toxoid (NeisVac-C®). 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. In

vaccinating countries, an infant may have 1 to 2 doses of meningococcal C conjugate vaccine during the first two years of life) (23).

Quadrivalent meningococcal A, C, W and Y vaccines conjugated to CRM197 (Menveo®) or tetanus toxoid (Nimenrix®) are also licensed in Europe, with Nimenrix® approved for use from 6 weeks of age, while Menveo® is only licensed from 2 years of age.

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 which is not licensed in Europe, 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.
Recommendations / National Immunization programs are heterogeneous in Europe, with some countries recommending only monovalent MenC vaccines in infancy/early childhood, while other countries have recently revised their recommendations to quadrivalent Men A, C, W, Y vaccines (some regions in Italy, NL*(24)

NeisVac-C® is considered the standard of care in several countries for meningococcal MenC vaccination in toddlers. So far none of the currently licensed meningococcal ACWY conjugate vaccines have been able to demonstrate non-inferiority of MenC immune response versus NeisVac-C®.

MenC has been one of the most important disease-causing serogroup in Europe and many countries in the world (eg, Australia, Brazil, and Canada), and is still circulating. Therefore, health authorities are reluctant to use a ACWY vaccine of which the MenC component has not been shown to be non-inferior to monovalent MenC-TT vaccine. However, epidemiology is changing with increasing notification rates of serogroups W & Y and a vaccine able to offer at least the same protection against MenC as monovalent MenC vaccine, while offering also a protection against other serogroups (W, Y) will provide an interesting option.

The purpose of MEQ00065 is to evaluate the investigational quadrivalent meningococcal MenACYW conjugate vaccine when used as a single dose toddler vaccine in individuals who are meningococcal vaccine naïve.

The study will aim to compare the immunogenicity of MenACYW conjugate vaccine versus quadrivalent MenACWY-TT conjugate vaccine, Nimenrix®, or versus monovalent MenC-TT conjugate vaccine, NeisVac-C®, and to describe the safety of 1 dose of MenACYW conjugate vaccine compared to 1 dose of Nimenrix® or to 1 dose NeisVac-C® in toddlers 12 to 23 months of age.

High titers for serogroup C were observed with MenACYW conjugate vaccine vs Nimenrix® in MET54 Phase II study and MET51 Phase III study. While the non-inferiority of seroresponse as measured by hSBA versus Nimenrix® was demonstrated, the statistical superiority of the MenC response of MenACYW conjugate vaccine was not tested as a primary objective in MET51 study. The proposed study will address statistical superiority of serogroup C titers vs Nimenrix® as part of the primary objective; other serogroups (A, W, Y) will not be evaluated.

2 Study Objectives

2.1 Primary Objectives

1) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. If the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) is demonstrated, then
   1.1) to demonstrate the non-inferiority of the antibody response (geometric mean titers [GMT]) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then
   1.2) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA. If the superiority of the antibody response (GMT) is demonstrated, then
   1.3) to demonstrate the superiority of the seroprotection rate to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA.
2) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by rSBA. If the non-inferiority of the seroprotection rate is demonstrated, then
   2.1) to demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by rSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then
   2.2) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by rSBA.

The endpoints for the primary objectives are presented in Section 9.1.

Overall, the primary objective for the study will be met if, objective 1) - non-inferiority of the seroprotection rate versus Nimenrix® as measured by hSBA, or objective 2) - non-inferiority of the seroprotection rate versus NeisVac-C® as measured by rSBA, is met.

2.2 Secondary Objectives

1) To demonstrate the non-inferiority of the seroprotection ate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA. If the non-inferiority of the seroprotection rate is demonstrated, then
   1.1) to demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate

vaccine or Nimenrix® as measured by rSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then

1.1.1) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or Nimenrix® as measured by rSBA

2) To demonstrate the non-inferiority of the seroprotection rate (antibody titers ≥ 1:8) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA. If the non-inferiority of the seroprotection rate is demonstrated, then

2.1) to demonstrate the non-inferiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA. If the non-inferiority of the antibody response (GMT) is demonstrated, then

2.1.1) to demonstrate the superiority of the antibody response (GMT) to meningococcal serogroup C following the administration of a single dose of MenACYW conjugate vaccine or NeisVac-C® as measured by hSBA.

The endpoints for the secondary objectives are presented in Section 9.2.

Overall, the secondary objective for the study will be met if objective 1) - non-inferiority of the seroprotection rate versus Nimenrix® as measured by rSBA, or objective 2) - non-inferiority of the seroprotection rate versus NeisVac-C® as measured by hSBA, is met.

2.3 Observational Objectives

Immunogenicity

1) To describe the antibody response to meningococcal serogroup C before and 30 days (+14 days) after vaccination in each group using hSBA in toddlers
2) To describe the antibody response to meningococcal serogroup C before and 30 days (+14 days) after vaccination in each group using rSBA in toddlers

Safety

To describe the safety profile of MenACYW conjugate vaccine, Nimenrix® and NeisVac-C®.

The endpoints for the observational objectives are presented in Section 9.3.

3 Investigators and Study Organization

This study will be conducted in approximately 31 centers in European countries. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator in each country. Details of the study 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 review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns.

Monitoring activities on sites will be conducted by the Sanofi Clinical Study Units (CSU) or a Contract Research Organization under the responsibility of Sanofi Pasteur. During the trial, clinical data reported in the electronic Case Report Books (CRBs) will be integrated into the clinical database under the responsibility of the Sanofi Pasteur Clinical Data Management (CDM) platform. Statistical activities will be performed under the responsibility of the Sponsor's Biostatistics Platform. Medical writing activities will be performed under the responsibility of the Sponsor's Medical Writing and Translation Platform.

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

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*s* (IEC*s*) or Institutional Review Board*s* (IRBs).

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

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

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This is a Phase III, modified double-blind, randomized, active-controlled, multi-center trial to compare the immunogenicity for serogroup C of a single dose of MenACYW conjugate vaccine to a single dose of Nimenrix® vaccine or NeisVac-C® vaccine in toddlers, 12 to 23 months of age.

A total of approximately 705 healthy toddlers aged 12 to 23 months who have not received any meningococcal vaccine during infancy, are planned to be enrolled and randomized to receive one dose of vaccine at Day (D) 0-Visit (V) 01, in one of the following 3 arms (1:1:1 ratio):

- Group 1: MenACYW conjugate vaccine
- Group 2: Nimenrix® vaccine (MenACWY-TT conjugate vaccine)
- Group 3: NeisVac-C® vaccine (MenC-TT conjugate vaccine)

All subjects will provide blood samples for immunogenicity assessment at V01 on D0 (pre-vaccination) and at V02 (30 to 44 days post-vaccination), which corresponds to the planned end of this study.

Solicited AE information will be collected for 7 days after vaccination, unsolicited AE information will be collected from D0 to D30, and SAE information, including adverse events of special interest (AESIs), will be collected throughout the trial.

5.1.2 Justification of the Study Design

This study is designed to evaluate the MenC immune responses and safety profiles following the administration of a single dose of the MenACYW conjugate vaccine in toddlers 12 to 23 months of age, compared to NeisVac-C® and Nimenrix® licensed vaccines.

In the MET51 pivotal Phase III study as well as in other studies to be included in the MenACYW conjugate vaccine Common Technical Dossier (CTD) for initial licensure, titers were measured by hSBA for the primary endpoint; the same assay will therefore be used in this study for the comparison to Nimenrix®. Titers measured by rSBA will also be compared as a secondary endpoint.

NeisVac-C® has been developed using rSBA testing method at Public Health England (PHE) laboratory and no references are available for titers measured by hSBA. In order to evaluate whether non-inferiority can be demonstrated, titers measured by rSBA generated in the same laboratory, PHE, should be used. Therefore, this study will use rSBA as the primary endpoint for the comparison to NeisVac-C®. Titers measured by hSBA will also be compared as a secondary endpoint.

In the countries where this study will be carried-out, the routine vaccination schedule does not include at the time of the study any vaccination against Meningococcal disease during the first year of life, which allows enrolment of naïve subjects.

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.

5.1.3 Study 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, NeisVac-C® 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 followed for safety from V01 on D0 to V02 after vaccination.

All subjects will be observed for 30 minutes after vaccination and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited AEs in the electronic case report book (eCRB) (see Section 9.3.2.3.1).

The subject's parent or other legally acceptable representative will record information in a diary card (DC) about solicited reactions from D0 to D7 after vaccination and unsolicited AEs will be recorded from D0 to D30.

Serious adverse events (SAEs, including adverse events of special interest [AESIs]) will be recorded in the DC throughout the study. The subject's parent / legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the study.

Study site staff will contact subjects' parent / legally acceptable representative by telephone on 8 days (+2 days) after V01 to identify the occurrence of any SAEs (including AESIs) not yet reported and to remind them to complete the DC and bring it back to V02.

The completed DC will be collected and reviewed with the subject's parent / legally acceptable representative at V02.

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. All information collected during the study visits must be recorded in the source documents. Some of the following information will also be recorded in the eCRF.

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

The Investigator or delegate will:

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 (see Section 5.2.4 and Section 5.2.5) for eligibility. Review vaccination history from the child's immunization record:
   a. Collect demographic data.
   b. Obtain verbal significant medical history about the subject, including ongoing medication.
   c. Take the subject's temperature (axillary, rectal, or oral, but axillary preferred) and record in the source document. If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.
   d. 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 week 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.
3) If subject satisfies all eligibility criteria, call the interactive response technology (IRT) for randomization (at least allocation of subject number and dose number of vaccine).
4) Obtain 4-milliliter (mL) of blood sample (BL0001) (see Section 7.1 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (after reasonable attempts as per local regulations) either the Visit 1 can be rescheduled to a later date at which point inclusion/exclusion criteria must be re-validated or the subject will be withdrawn from the study without being vaccinated. If during the rescheduled visit the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.

The unblinded qualified study staff member will:

5) 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 = MenACYW conjugate vaccine

   Group 2 = Nimenrix®

   Group 3 = NeisVac-C®

   and record the date, the site, side, the route of injection, and the dose number. Affix the vaccine label(s) into the subject's source documents.

The Investigator or delegate will:

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

7) Give the subject's parent/legally acceptable representative:

   - a DC, to record any injection site reactions and systemic adverse events, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs
   - a thermometer, for temperature measurement
   - and a ruler, to measure the size of any injection site reaction

   and go over the instructions for their use.

8) Remind the subject's 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).

9) Remind the subject's parent/legally acceptable representative to notify the site in case of an SAE.

10) Complete the source documents and relevant eCRF pages for this visit.

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

Note: If D8 falls on a weekend or a holiday, the TC may be made on the following business day.

The Investigator or an authorized designee will:

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

2) Remind the subject's parent/legally acceptable representative to do the following:
   - Complete the D0 to D7 pages of the DC
   - Complete the remaining pages of the DC, and bring them on V02 (D30 + 14 days)
   - Notify the site in case of an SAE

3) Confirm the date of the next visit.

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

The Investigator or delegate will:

1) Review and collect the pages of the DC (for clarity, content, and completeness) with the subject's parent/legally acceptable representative, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.

2) Review temporary contraindications for V02 blood sampling (see Section 5.2.8).
3) Obtain the second 4 mL blood sample (BL0002) (see Section 7.1 for detailed instructions regarding the handling of blood samples).

   Note: If the attempt to collect blood is unsuccessful, the subject should be given the opportunity for another attempt within the protocol time windows. If ultimately a blood sample cannot be obtained, the reason will be recorded in the electronic CRB.
4) Complete the source documents, relevant CRF pages including the end of study record.
5) If 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's parent/legally acceptable representative by telephone. During the TC, the subject's legally acceptable representative will be reminded to return the DC to the study site. TCs will be documented on the Telephone/Interview Record. If the study personnel are unable to contact the subject's parent/legally acceptable representative with 3 attempts, the study personnel will follow instructions given in Section 5.2.10.

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

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

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

5.1.5 Planned Study Calendar

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

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject): Q3 2019 to Q4 2020

Planned inclusion period - FVFS to FVLS (first visit, last subject): Q3 2019 to Q4 2020

Planned vaccination period: Q3 2019 to Q4 2020

Planned end of study: Q4 2020

Planned date of final clinical study report: Q2 2021

5.2 Enrollment and Retention of Study 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 may be invited to enroll the subject in the trial, if eligible. Subjects may also be recruited from the general population.

Recruitment procedures and materials will be submitted to the IEC/IRB for approval before implementation. Recruitment will be conducted in a competitive manner.

5.2.2 Informed Consent Procedures

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

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

The actual ICF used at each center may differ, depending on local regulations and 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/legally acceptable representative's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

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:

MEQ00065 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 to be eligible for study enrollment:

1) Aged 12 to 23 months on the day of the first study visit[a].
2) ICF has been signed and dated by the parent(s) / legally acceptable representative(s).
3) Subject and parent / legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures.
4) Covered by health insurance if required by local regulations.

5.2.5 Exclusion Criteria

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

1) Participation in the 4 weeks (28 days) preceding the study vaccination or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.
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 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) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B vaccine).
5) 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).
6) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically.
7) 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).

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

8) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances[a].
9) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine.
10) Personal history of Guillain-Barré syndrome (GBS).
11) Thrombocytopenia, as reported by the parent/ legally acceptable representative or suspected thrombocytopenia contraindicating intramuscular vaccination in the Investigator's opinion.
12) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion.
13) Chronic illness[b] that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion.
14) 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.
15) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw.
16) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.

According to local regulations, if the subject has a primary physician who is not the Investigator, the site may contact this physician to inform him/her of the subject's participation in the study.

5.2.6 Medical History

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

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

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

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

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[a] The components of the vaccines used in the study are listed in Section 6.1 and in the Investigator's Brochure.

[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.

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

5.2.7 Contraindications for Subsequent Vaccinations

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

5.2.8 Temporary 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 study at any time. A subject may be withdrawn from the study:

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

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

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

Withdrawn subjects will not be replaced, with the following exception: As a consequence of the COVID-19 hold, approximately 30 subjects were identified to be excluded from the PPAS as they were unable to complete their follow-up visit as planned in the protocol. To maintain the planned study power and the randomization ratio, approximately 30 additional subjects are planned to be enrolled.

In the event of any new unexpected situations impacting study visits, the sample size might be increased to replace subjects excluded from the PPAS.

5.2.10 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (ie, documented TCs and certified mail) should be undertaken to locate or recall them, or at

least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents.

5.2.11 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.3.2. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the parent/legally acceptable representative cannot be found or contacted in spite of efforts to locate him/her before the date of their child planned last visit, as outlined in Section 5.2.10. The certified letter was sent by the Investigator and returned unsigned, and the parent/legally acceptable representative did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant non-compliance with the protocol (e.g., deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration) • If the subject experiences a definitive contraindication that is not an SAE or AE • If the parent/legally acceptable representative signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit
Withdrawal by Subject or Parent / Legally Acceptable Representative	To be used: • When the parent/legally acceptable representative indicated unwillingness to continue in the study • When the parent/legally acceptable representative made the decision to discontinue his/her child participation in the study for any personal reason other than an SAE/AE (e.g., parent/legally acceptable representative is relocating, inform consent withdrawal, etc.)

5.2.12 Follow-up of Discontinuations

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

For subjects where the reason for early termination was lost to follow-up or if the subject's parent/legally acceptable representative withdrew their 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 Modification of the Study and Protocol

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

An administrative / non-substantial amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. In case of non-substantial amendment, IECs / IRBs have to be notified.

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

5.3.1 Amendment Justification

Amendment 1

Due to the COVID-19 pandemic, subject enrollment was put on hold on 17 March 2020.

As this is a one-dose schedule, no ongoing participants were expected to receive further vaccination. The decision for each individual participant to remain in the study was to be made on a case by case basis based on the investigator's best medical judgement and the evolving situation at each site. Participants who could not be followed up as per protocol or could be followed up but out of the protocol defined window period, were to be kept in the study till the end of the study period and not automatically withdrawn from the study. Safety follow up could be accomplished via phone contact if an office or home visit was not possible.

These measures were taken by the Sponsor to ensure the well-being of subjects (ie, to limit exposure to COVID-19) and were implemented without IRB/EC approval, as per national and international guidance. However, IRB/EC and health authorities were informed promptly about the measures reported in the current amendment.

After ensuring subject safety, and with national health authority approval, enrollment will resume.

In the current amendment, the Sponsor will increase the sample size of the study to replace subjects excluded from the PPAS (see Section 12.5) to ensure the adequate power to fulfill the endpoints (see Section 9).

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by applicable regulatory

requirements. The Investigator shall promptly inform the study subject's parents/legally acceptable representatives and should assure appropriate subject therapy and/or follow-up.

6 Products Administered

6.1 Identity of the Investigational Products

6.1.1 Identity of Study Product

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

Form: Liquid solution

Dose: 0.5 mL

Route: IM

Batch number: To be determined

Composition: Each 0.5 mL dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following components:

Meningococcal capsular polysaccharides:

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

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

6.1.1.1 Preparation and Administration

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

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

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

The site of IM injection should be prepared with a suitable antiseptic prior to administration of 1 dose (0.5 mL) of MenACYW conjugate vaccine. After vaccine administration, the used syringe and needle will be disposed of in accordance with currently established guidelines.

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

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

6.1.1.2 Dose Selection and Timing

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

6.1.2 Identity of the Control Products

6.1.2.1 Nimenrix®

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

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

6.1.2.1.1 Composition

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

N meningitidis polysaccharides:

Serogroup A.....5 µg
Serogroup C.....5 µg
Serogroup 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 injections

6.1.2.1.2 Preparation and Administration

Nimenrix® is supplied as a white powder or cake in a single dose glass vial and a clear and colorless solvent in a pre-filled syringe. The supplied solvent is used to reconstitute the powder in the vial.

After reconstitution, a single dose of Nimenrix® should be administered by IM injection. See the Nimenrix® EU SmPC for additional information on preparation of the reconstituted dose (22).

The procedures for preparing and administering this control product are the same as those described for the study product in Section 6.1.1.1.

6.1.2.1.3 Dose Selection and Timing

All subjects in Group 2 will receive 1 dose of Nimenrix® vaccine on V01 (D0).

6.1.2.2 NeisVac-C®

NeisVac-C®: Meningococcal Group C Polysaccharide Conjugate Vaccine Adsorbed (Pfizer Limited, Sandwich, UK)

Form: Suspension for injection in a pre-filled syringe

Dose: 0.5 mL

Route: IM

Batch number: Commercial lot to be supplied by Sponsor

6.1.2.2.1 Composition

Each 0.5 mL dose of NeisVac-C® vaccine is formulated to contain:

Neisseria meningitidis serogroup C (strain C11) polysaccharide (de-O-acetylated). .... 10 µg
conjugated to tetanus toxoid..... 10-20 µg
adsorbed on aluminium hydroxide, hydrated..... 0.5 mg Al3+

Excipients: Sodium chloride, Water for injections

6.1.2.2.2 Preparation and Administration

NeisVac-C® is supplied as a suspension for injection in a pre-filled syringe.

A single dose of NeisVac-C® should be administered by IM injection. See the NeisVac-C® EU SmPC for additional information (21).

The procedures for preparing and administering this control product are the same as those described for the study product in Section 6.1.1.1.

6.1.2.2.3 Dose Selection and Timing

All subjects in Group 3 will receive 1 dose of NeisVac-C® vaccine on V01 (D0).

6.2 Identity of Other Product(s)

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® and NeisVac-C® vaccines 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 to determine the dates and times of delivery of products.

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

6.3.2.2 Product Storage

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

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

6.3.2.3 Product Accountability

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

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

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

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

6.3.3 Replacement Doses

If a replacement dose is required (eg, because the syringe/vial broke or particulate matter was observed in the syringe/vial), the site personnel must 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 study period.

6.3.5 Recall of Products

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

6.4 Blinding and Code-breaking Procedures

The MEQ00065 study is modified double-blind, which means that both the subject and the Investigator remain unaware of the treatment assignments throughout the study. An unblinded vaccine administrator will administer the appropriate vaccine but will not be involved in safety data collection. The Sponsor and laboratory personnel performing the serology testing will also remain blinded to treatment assignments throughout the study until database lock.

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

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

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

[a] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

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

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and whose parent/ legally acceptable representative signs the ICF will be randomly assigned to Groups 1 through 3 in a 1:1:1 ratio, such that Groups 1 to 3 will have approximately 235 subjects each.

Unblinded vaccine administrator will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide at least the subject number and vaccine dose number. The full detailed procedures for group and dose allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the study, then the information will only be recorded on the subject recruitment log.

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

For example:

Subject 246000100005 is the fifth subject enrolled in Center Number 1 in Finland (246 being the Finland country code).

Subject 208001400006 is the sixth subject enrolled in Center Number 14 in Denmark (208 being the Denmark country code).

Subject 276002300005 is the fifth subject enrolled in Center Number 23 in Germany (276 being the Germany country code).

Subject numbers should not be reassigned for any reason. The randomization lists of subjects will be stratified by Center. The randomization codes will be kept securely in the IRT.

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications and other therapies (eg, blood products) should be recorded in the source document. All new medications prescribed for new medical conditions / AEs during study participation should also be recorded in the source document.

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

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

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

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

Category 1 medications will be reported in the CRB from the day of first vaccination to the end of the solicited and unsolicited follow-up period after each vaccination.

- Category 2: Reportable medications with potential impact on immune response of the study vaccines and used to define the PPAS. For example:
    a. Influenza and other non-study vaccines: Influenza vaccine in the 2 weeks (14 days) preceding the trial vaccination up to the last blood draw and any other vaccines (other than the study vaccine) in the 4 weeks preceding the trial vaccination up to the last blood draw
    b. Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
    c. Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) within past 3 months, anti-cancer chemotherapy, anti-proliferative drugs such as DNA synthesis inhibitors, or radiation therapy: used in the 6 months preceding the first trial vaccination, and up to the last blood draw.

Category 2 medications will be reported in the CRB according to the collection period detailed above up to the last blood draw.

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

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

Medications should be collected as concomitant if there is a reasonable possibility that they may still impact on safety and/or immune assessment, even when the treatment was stopped before collection (eg medications characterized by long half-life, dose accumulation, or which might cause delayed adverse reactions).

Additionally, given the COVID-19 pandemic and the possible use of medications with or without medical prescription, medications that interfere with the immune response should be actively evaluated.

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

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

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

Dosage and administration route, homeopathic medication, will not be recorded. If the subject has received medications other than those listed in Categories 1, 2, and 3, the detailed information will be collected in the source documents only.

Medications given to treat an AE (medication(s) prescribed for preventing AE occurrence (e.g. paracetamol to reduce the risk of fever)) will be captured in the "Action Taken" section of the AE CRB only. No details will be recorded in the concomitant medication CRB unless the medication(s) received belongs to one of the prelisted categories.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at Visits V01 and V02. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At Visits V01 and V02, 4 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 as well as the assigned subject's number and sampling stage on the pre-printed label and will attach the label to the tube. When vaccination and blood sample collection occur at the same visit and vaccine is given only in one of the arms, blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

If attempts to obtain the first blood draw are unsuccessful (after reasonable attempts as per local regulations) then V01 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 immune response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

After the blood draw, gently invert the tube several times. Then allow the tube to clot by standing it vertically at room temperature for 60 to 120 minutes (no more and no less) prior to centrifuging.

The maximum amount of time the blood can stand at room temperature in the upright position is 2 hours. If the time between blood sampling and centrifugation is longer than 2 hours, the vacutainer should be refrigerated at 2°C to 8°C after the period of clotting at room temperature. The sample must be centrifuged within 24 hours from the initial blood draw time.

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

7.3 Sample Storage and Shipment

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

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

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

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.

Subjects' 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 existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

8 Clinical Supplies

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

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

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and/or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and for the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

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

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

1) Antibody titers against meningococcal serogroup C measured by hSBA,30 days (+ 14 days) after vaccination:
   - ≥ 1:8, with MenACYW conjugate vaccine or Nimenrix®
   - With MenACYW conjugate vaccine or Nimenrix®
2) Antibody titers against meningococcal serogroup C measured by rSBA, 30 days (+ 14 days) after vaccination:
   - ≥ 1:8, with MenACYW conjugate vaccine or NeisVac-C®
   - With MenACYW conjugate vaccine or NeisVac-C®

9.1.1.2 Immunogenicity Assessment Methods

All assays will be performed at GCI, Swiftwater, Pennsylvania (PA) or at a qualified contract laboratory for GCI unless otherwise stated.

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

Antibodies to meningococcal antigens (hSBA Method)

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

Antibodies to Meningococcal Antigens (rSBA method)

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

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

The secondary endpoints for the evaluation of immunogenicity are:

1) Antibody titers against meningococcal serogroup C measured by rSBA, 30 days (+ 14 days) after vaccination:
   - ≥ 1:8, with MenACYW conjugate vaccine or Nimenrix®
   - With MenACYW conjugate vaccine or Nimenrix®
2) Antibody titers against meningococcal serogroup C measured by hSBA, 30 days (+ 14 days) after vaccination:
   - ≥ 1:8 with MenACYW conjugate vaccine or NeisVac-C®
   - With MenACYW conjugate vaccine or NeisVac-C®

9.2.1.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 9.1.1.2.

9.2.2 Safety

There are no secondary objectives for safety.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 Immunogenicity Endpoints

The observational endpoints for the evaluation of immunogenicity are:

Observational Objective 1:

Antibody titer against meningococcal serogroup C measured by hSBA in each group:

- Assessed before and at 30 days (+ 14 days) after vaccination
- ≥ 1:4 and ≥ 1:8, assessed at 30 days (+ 14 days) after vaccination
- Post-vaccination/pre-vaccination titers ratio
- ≥ 4-fold rise from pre-vaccination to post-vaccination
- Vaccine seroresponse measured by hSBA, with seroresponse defined as:
  - For a subject with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16
  - For a subject with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer.

Observational Objective 2:

Antibody titers against meningococcal serogroup C measured by rSBA in each group:

- Assessed before and at 30 days (+ 14 days) after vaccination
- ≥ 1:8 and ≥ 1:128, assessed before and at 30 days (+ 14 days) after vaccination
- Post-vaccination/pre-vaccination titers ratio
- ≥ 4-fold rise from pre-vaccination to post-vaccination
- Vaccine seroresponse measured by rSBA, with seroresponse defined as:
  - For a subject with pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32
  - For subjects with pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer.

9.3.1.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the observational endpoints are the same as those presented in Section 9.1.1.2.

9.3.2 Safety

9.3.2.1 Safety Definitions

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

Adverse Event (AE):

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

Therefore, an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic

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

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

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

bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new-onset diabetes, or autoimmune disease.

Adverse Reaction (AR):

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

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

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

Solicited Reaction:

A solicited reaction is an "expected" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRB (eg, injection site tenderness occurring between D0 and D7 post-vaccination).

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

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

The assessment of these reactions by the Investigator is mandatory.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions pre-listed in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D7 is a solicited reaction (ie, pre-listed in the protocol and CRB), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

An AESI is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

9.3.2.2 Safety Endpoints

The safety profile of the 3 vaccines will be evaluated within 30 days (+ 14 days) after the vaccination. The following observational endpoints for the evaluation of safety are:

- Unsolicited systemic AEs reported in the 30 minutes following the vaccination
- Solicited (pre-listed in the subject diary and the electronic CRF) injection site reactions and systemic reactions starting anytime from D0 (Day of vaccination) through D7 after the vaccination
- Unsolicited (spontaneously reported) non-serious AEs between D0 and D30
- SAEs (including AESIs) throughout the study, ie, from D0 to Visit 2

Depending on the items, the endpoints recorded or derived could include:

Nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to vaccine, whether the AE led to early termination from the study, seriousness criterion, outcome.

9.3.2.3 Safety Assessment Methods

At V02, the Investigator or a delegate will perform a clinical or medically-driven physical examination, and will ask the subject's parent(s)/legally acceptable representative(s) about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.3.2.3.1 Immediate Post-vaccination Observation Period

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

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected)
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination
- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10.

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

After vaccination of subjects, subject's parent(s)/legally acceptable representative(s) will be provided with a diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (ie, Day 0 through Day 7) until resolution:

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

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

- None
- Medication
- Health care provider contact
- Hospitalized

The subject's parent(s)/legally acceptable representative(s) 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 TC 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 pre-listed in the diary cards and CRB, together with the intensity scales.

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

CRB term (MedDRA lowest level term [LLT])	Injection site tenderness	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition	Pain when the injection site is touched or injected limb mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3: Cries when injected limb is mobilized, 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, subject's parent(s)/legally acceptable representative(s) will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

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

CRB term (MedDRA lowest level term [LLT])	Fever	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 (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined 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 **or** ≥ 100.4°F to ≤ 101.3°F	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 **or** > 101.3°F to ≤ 103.1°F	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 **or** > 103.1°F	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, subject's parent(s)/legally acceptable representative(s) will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

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

9.3.2.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, parent(s)/legally acceptable representative(s) will be instructed to record any other medical events that may occur during the 30 days (+ 14 days) period after vaccination. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from D0 to Visit 2 (ie, between D0 and D30 (+ 14 days)). Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports. In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE.
See Section 10 for further details on SAE reporting.

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

- Start and stop dates[a]
- Intensity of the event:

  For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.1 and Table 9.2).

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

  - Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

[a] The stop date of all related AEs will be actively solicited. For other events, the investigator will provide the stop date when it becomes available. AEs for which no stop date was obtained during the course of the study will be considered as ongoing at the end of the study.

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

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

- Action taken for each AE (eg, medication)

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

- None
- Medication
- Health care provider contact
- Hospitalized

- Whether the AE was serious

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

9.3.2.3.4 Adverse Events of Special Interest

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

- Generalized seizures (febrile and non-febrile) (25, 26)
- Kawasaki disease (27-29)
- GBS (30)
- Idiopathic thrombocytopenic purpura (ITP) (31, 32)

These events have been listed as AESIs based on the feedback received from the EU regulators. No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in the completed clinical studies. Due to their medical importance and to ensure expedited communication to the Sponsor, these AESIs are to be considered as SAEs and reported to the Sponsor according to the procedure described in Section 10. Further instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

9.3.2.3.5 Assessment of Causality

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

Not related – The AE is clearly/most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening Phase, if applicable)

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

Note: By convention, all AEs reported at the injection site (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

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

9.3.3 Efficacy

No clinical efficacy data will be obtained in the study.

10 Reporting of Serious Adverse Events

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

10.1 Initial Reporting by the Investigator

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

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

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

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

- By fax, to the following number: +1 (570) 957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
- By express mail, to the following address:
  Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global Pharmacovigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370

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

If there is need for urgent consultation, the Investigator is to contact the RMO. If the RMO cannot be reached, the Investigator may contact the Local Medical Officer as described in the Operating Guidelines.

10.2 Follow-up Reporting by the Investigator

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

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

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

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

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.3.2.3.5.

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

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

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs according to the Directive 2001/EC article 17. The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions (SUSARs) that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee(s), and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. All other SUSARs will be reported to the competent authorities concerned and to the Ethics Committee(s) concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

The Sponsor's RMO will also notify the Investigators in writing of the occurrence of any reportable SAEs.

Once a year throughout the clinical trial, the sponsor will provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee(s) with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.3.2.3. These diary cards will include pre-listed 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.

At specified intervals, the Investigator or an authorized designee will interview the parents/legally acceptable representatives to collect the information recorded in the diary card and will attempt to clarify anything that is incomplete or unclear.

Participant race and ethnicity will be collected in this study because these characteristics may influence the immune response to the vaccine.

All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of the Sponsor, using a validated Electronic Records/Electronic Signature-compliant platform (21 CFR Part 11).

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

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

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

11.2 Data Management

Management of SAE Data

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

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

Management of Clinical and Laboratory Data

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

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

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

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

11.3 Data Review

A 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 on a blinded manner. Periodic safety data review will be performed by the Sponsor's SMT.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

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

12.1.1.1 Hypotheses

12.1.1.2 Statistical Methods

The immunogenicity of MenACYW conjugate vaccine serogroup C will be compared to that of Nimenrix® vaccine and to that of NeisVac-C® vaccine using sequential testing approaches.

Non-Inferiority

A non-inferiority testing approach will be used to compare post-vaccination (ie, 30 days after the vaccination) seroprotection rates and GMTs of MenACYW conjugate vaccine to that of Nimenrix® and NeisVac-C®, using a two-sided 97.5% Confidence Interval (CI) with the following hypotheses:

For seroprotection rates:

$$H_0 : \pi_{\text{MenACYW}} - \pi_{Comparator} \leq -0.1$$

$$H_1 : \pi_{\text{MenACYW}} - \pi_{Comparator} > -0.1$$

Or

For GMTs

$$H_0 : GMT_{\text{MenACYW}} / GMT_{Comparator} \leq 1/\delta$$

$$H_1 : GMT_{\text{MenACYW}} / GMT_{Comparator} > 1/\delta$$

with:

- Comparator: Nimenrix® or NeisVac-C®
- π: seroprotection rates
- δ: non-inferiority margin set at 1.5

Superiority

If the non-inferiority testing succeeds then a superiority approach will be used to compare post-vaccination (ie, 30 days after the vaccination) seroprotection rates and/or GMTs of MenACYW conjugate vaccine to that of Nimenrix® and NeisVac-C®, using a two-sided 97.5% CI with the following hypotheses:

For seroprotection rates

$$H_0 : \pi_{\text{MenACYW}} - \pi_{Comparator} \leq 0$$

$$H_1 : \pi_{\text{MenACYW}} - \pi_{Comparator} > 0$$

Or

For GMTs

$$H_0 : GMT_{\text{MenACYW}} / GMT_{Comparator} \leq 1$$

$$H_1 : GMT_{\text{MenACYW}} / GMT_{Comparator} > 1$$

with:

- Comparator: Nimenrix® or NeisVac-C®
- π: seroprotection rates

For the seroprotection rates, the 97.5% CI of the difference in proportions will be computed using the Wilson Score method without continuity correction (Newcombe method).

For the GMTs, the two-sided 97.5% CI of the ratio of post-vaccination GMTs will be calculated using normal approximation of log-transformed titers.

The non-inferiority will be demonstrated against seroprotection rates if the null hypothesis is rejected, ie, if the lower limit of the two-sided 97.5% CI for the difference between the seroprotection rates is > -10%.

The non-inferiority will be demonstrated against GMTs if the null hypothesis is rejected, ie, lower limit of the two-sided 97.5% CI for the ratio of GMTs > 1/1.5.

The superiority will be demonstrated against seroprotection rates if the null hypothesis is rejected, ie, if the lower limit of the two-sided 97.5% CI for the difference between the seroprotection rates is > 0%.

The superiority will be demonstrated against GMTs if the null hypothesis is rejected, ie, lower limit of the two-sided 97.5% CI for the ratio of GMTs > 1.

The testing approach will be done in parallel and using a step by step approach for the 2 comparators (3 steps):

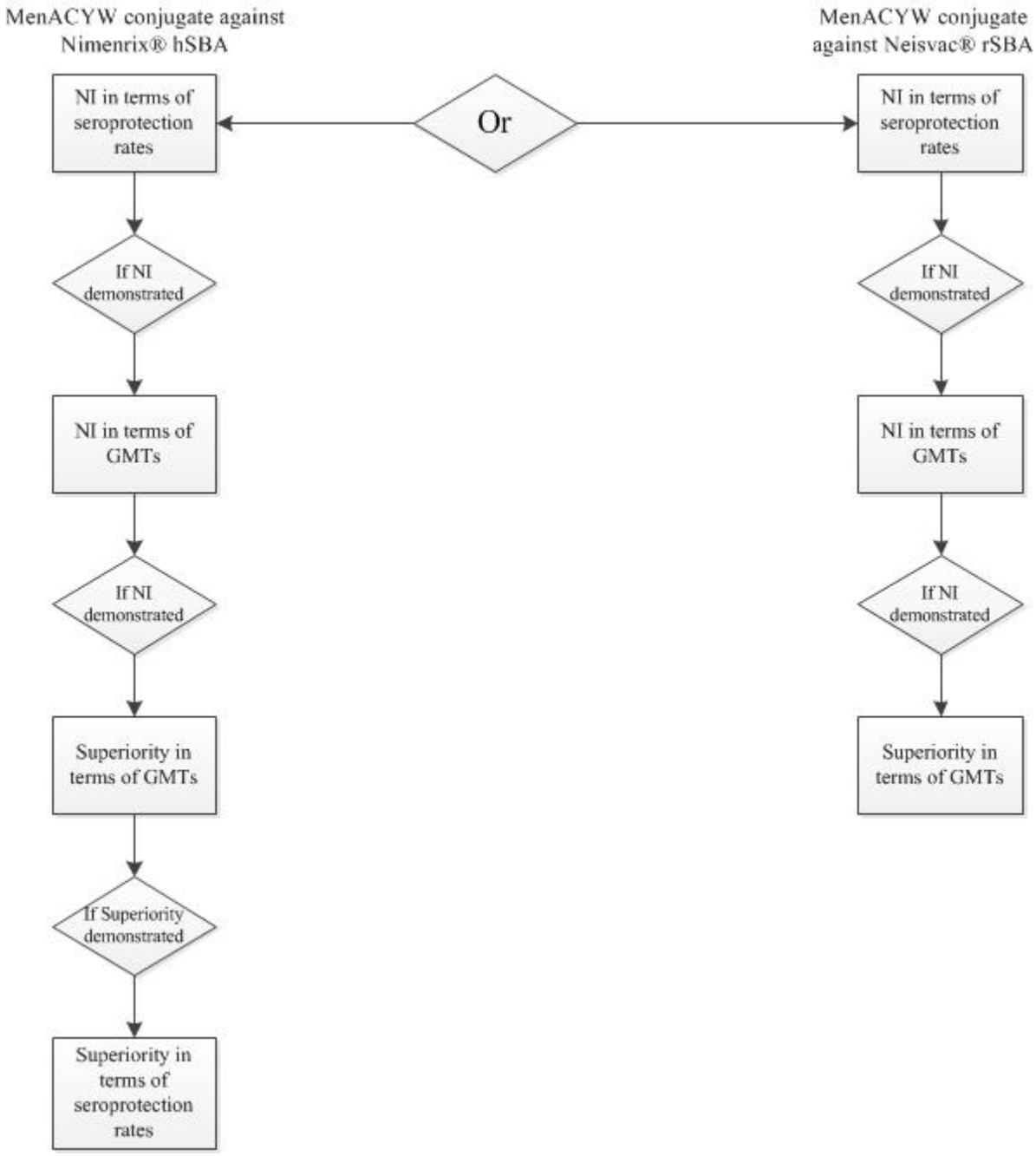
Nimenrix®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against Nimenrix® measured by hSBA is demonstrated then the non-inferiority using hSBA GMTs will be tested. If the non-inferiority using hSBA GMTs of MenACYW conjugate against Nimenrix® is demonstrated then the superiority using hSBA GMTs will be tested. If the superiority using hSBA GMTs is demonstrated then the superiority using hSBA seroprotection rates will be tested.

NeisVac-C®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against NeisVac-C® measured by rSBA is demonstrated then the non-inferiority using rSBA GMTs will be tested. And if the non-inferiority using rSBA GMTs is demonstrated then the superiority using rSBA GMTs will be tested.

Figure 1: Sequential statistical testing approach for primary objectives



To conclude, non-inferiority using seroprotection rates of MenACYW conjugate against Nimenrix® measured by hSBA or non-inferiority using seroprotection rates of MenACYW conjugate against NeisVac-C® measured by rSBA have to be demonstrated.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Hypotheses

12.1.2.2 Statistical Methods

A similar statistical approach as for the primary objective will be used considering the rSBA antibody titers for Nimenrix® and hSBA antibody titers for NeisVac-C®.

The testing approach will be done in parallel and using a step by step approach for the 2 comparators (3 steps):

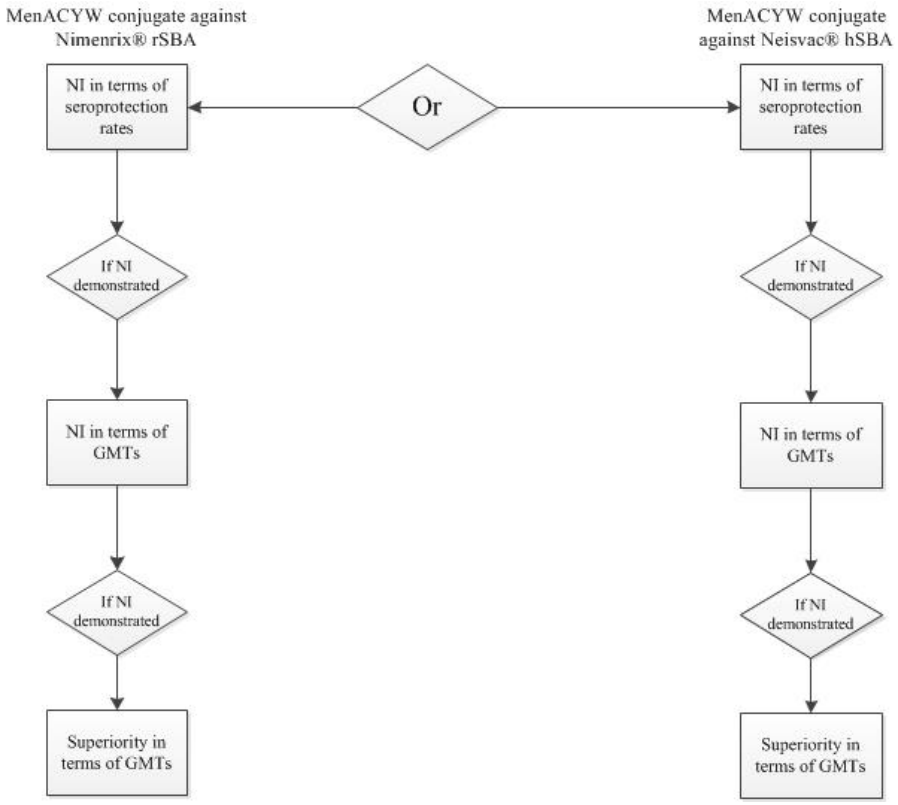
Nimenrix®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against Nimenrix® measured by rSBA is demonstrated then the non-inferiority using rSBA GMTs will be tested. If the non-inferiority using rSBA GMTs of MenACYW conjugate against Nimenrix® is demonstrated then the superiority using rSBA GMTs will be tested.

NeisVac-C®:

If the non-inferiority using seroprotection rates of MenACYW conjugate against NeisVac-C® measured by hSBA is demonstrated then the non-inferiority using hSBA GMTs will be tested. And if the non-inferiority using hSBA GMTs is demonstrated then the superiority using hSBA GMTs will be tested.

Figure 2: Sequential statistical testing approach for secondary objectives



To conclude, non-inferiority using seroprotection rates of MenACYW conjugate vaccine against Nimenrix® measured by rSBA or non-inferiority using seroprotection rates of MenACYW conjugate vaccine against NeisVac-C® measured by hSBA have to be demonstrated.

12.1.3 Statistical Methods for Observational Objectives

For immunogenicity and safety observational objectives, the descriptive analyses will be done according to each vaccine group. The main parameters will be described with 95% CI using the exact binomial distribution (Clopper-Pearson method) for proportions and using the normal approximation of the Log_{10} concentrations/titers, followed by a back transformation for GMTs.

The main parameters for observational objectives are:

Immunogenicity Observational Objective 1: Antibody titer against meningococcal serogroup C by hSBA in each group:

- GMTs before and at 30 days (+ 14 days) after vaccination
- Percentage of subjects with antibody titers ≥ 1:4 and ≥ 1:8, assessed at baseline and 30 days (+14 days) after vaccination
- Post-vaccination/pre-vaccination GMTR of titers
- Percentage of subjects with a ≥ 4-fold rise from pre-vaccination to post-vaccination

- Vaccine seroresponse rate, with a seroresponse defined as:
    - For a subject with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16
    - For a subject with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer

Immunogenicity Observational Objective 2: Antibody titers against meningococcal serogroup C measured by rSBA

- GMTs before and at 30 days (+ 14 days) after vaccination
- Percentage of subjects with antibody titers ≥ 1:8 and ≥ 1:128, assessed before and at 30 days (+ 14 days) after vaccination in each group
- Post-vaccination/pre-vaccination GMTR of titers
- Percentage of subjects with a ≥ 4-fold rise from pre-vaccination to post-vaccination
- Vaccine seroresponse rate, with a seroresponse defined as:
    - For a subject with pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32
    - For subjects with pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer

Reverse cumulative distribution curves (RCDCs) figures will also be provided.

Safety Observational Objective:

The following parameters will be used in each group for the evaluation of safety: counts, percents and 95%Cis as well as number of AEs when considered of interest for each of the followings:

- Unsolicited systemic AEs reported in the 30 minutes following the vaccination
- Solicited injection site reactions and systemic reactions starting anytime from D0 through D7 after the vaccination
- Unsolicited non-serious AEs up to D30 after the vaccination
- SAEs (including AESIs) up to D30 after the vaccination and throughout the study, ie, from D0 to Visit 2

Depending on the items, the parameters could be detailed according to:

Nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to vaccine, whether the AE led to early termination from the study, seriousness criterion, outcome.

12.2 Analysis Sets

Four main analysis sets will be used in the study: the full analysis set (FAS), 2 per protocol analysis sets (PPAS) and the safety analysis set (SafAS).

12.2.1 Full Analysis Set

The FAS is defined as the subset of randomized subjects who received one dose of study vaccine. Subjects will be analyzed according to the vaccine treatment group to which they were randomized.

12.2.2 Per-Protocol Analysis Sets

The PPAS are subsets of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from all 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 provide post-dose serology sample at V02 in the proper time window (ie, D30 + 14 days) or the post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy/medication/vaccine as defined in Section 6.7
- Subject had other protocol violations or deviations that affected the subject's immune response, as determined by the clinical team before locking the database

In addition to the reasons listed above, subjects will also be excluded from the hSBA PPAS if:

2.2) Subject post-dose serology sample at V02 did not produce a valid test result (ie, hSBA result is missing or not reported)

And from the rSBA PPAS if:

2.3) Subject post-dose serology sample at V02 did not produce a valid test result (ie, rSBA result is missing or not reported)

Subjects will be analyzed according to the vaccine treatment group to which they were randomized.

12.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received one dose of study vaccine. All subjects will have their safety analyzed according to the vaccine they actually received.

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

12.2.4 Populations Used in Analyses

The primary immunogenicity analyses will be performed on the hSBA PPAS for comparisons to Nimenrix® and on the rSBA PPAS for comparisons to NeisVac-C® and will be confirmed on the FAS.

The secondary immunogenicity analyses will be performed on the rSBA PPAS for comparisons to Nimenrix® and on the hSBA PPAS for comparisons to NeisVac-C® and will be confirmed on the FAS.

Observational objectives on immunogenicity will be performed on the PPASs and the FAS.

Observational objectives on safety will be performed on the SafAS.

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-dose computed value divided by baseline computed value

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

12.3.3 Efficacy

No clinical efficacy data will be obtained in the study.

12.4 Interim / Preliminary Analysis

No interim or preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

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13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Study / Good Clinical Practice

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

13.2 Source Data and Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent form, telephone contact logs, and worksheets.

The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

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

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

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

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

13.3 Confidentiality of Data and Access to Subject Records

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

Sanofi Pasteur personnel (or designates), the IECs / IRBs, and regulatory agencies, including the 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.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the study (i.e., before the inclusion of the first subject), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the site; and that the study Investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the Sponsor's

[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.

procedures. Specific training sessions for the study Investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

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

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

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

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

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

13.4.2 Audits and Inspections

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

13.4.3 Archiving

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

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

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

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

13.5 Financial Contract and Insurance Coverage

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

13.6 Stipends for Participation

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

13.7 Publication Policy

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

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

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

14 Reference List

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15 Signature Page

Sponsor Signature

I confirm that this protocol (version 4.0 dated 15 May 2020) is in accordance with applicable regulations and Good Clinical Practice.

Function	Name	Date	Signature
Sponsor's Responsible Medical Officer	[redacted]		
Project Manager and Study Leader			