NCT Number:NCT03476135

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered as a Booster Dose in Children Vaccinated 3 Years Earlier as Toddlers

A Phase III, open-label, multi-center study to describe the immune persistence of the priming dose and describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine in children in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix® as part of the MET54 study.

Clinical Study Protocol, Amendment 1

Health Authority File Number:	EudraCT #: 2017-001993-40
WHO Universal Trial Number (UTN):	U1111-1183-5988
Study Code:	MET62
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular (IM)
Indication For This Study:	Meningococcal conjugate vaccine as a booster dose in children vaccinated 3 years earlier as toddlers
Manufacturer:	Same as Sponsor
Coordinating Investigator	[redacted]
Sponsor's Responsible Medical Officer:	[redacted] Sanofi Pasteur Inc. Tel: E-mail:
Pharmacovigilance Global Safety Expert:	[redacted] Sanofi Pasteur Inc. Tel: E-mail:
Clinical Trial Manager:	[redacted] Tel: E-mail:
Version and Date of the Protocol:	Version 2.0 dated 15 March 2018

History of Protocol Versions

Table 1: Previous versions of the protocol

Version*	Date	Comments
1.0	24 August 2017	Original study protocol (first version used in the study)

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

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Synopsis

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

Title of the Trial:	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered as a Booster Dose in Children Vaccinated 3 Years Earlier as Toddlers
Development Phase:	Phase III
Coordinating Investigator:	[redacted]
Trial Centers:	This will be a multi-center trial conducted at approximately 8 sites in Finland. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	1Q 2018 to 4Q 2018
Trial Design and Methodology:	A Phase III, open-label, multi-center study to describe the immune persistence of the priming dose and describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine in children in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix® as part of the MET54 study. Subjects who were vaccinated 3 years (± 45 days) earlier at 12 to 23 months of age in study MET54 will be eligible for enrollment in study MET62. All subjects will receive a single dose of MenACYW conjugate vaccine on Day (D) 0. All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days after vaccination. Solicited adverse event (AE) information will be collected for 7 days after vaccination; unsolicited AE information will be collected from Visit 1 (D0) to Visit 2 (D30 [+14 days]), and serious adverse event (SAE) information (including adverse events of special interest [AESIs]) will be collected throughout the study period.
Objectives:	***Immunogenicity*** 1) To describe the antibody persistence of meningococcal serogroups A, C, Y, and W before a booster dose in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers 2) To describe the antibody responses to meningococcal serogroups A, C, Y, and W 30 days after a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

	3) To describe the antibody responses against tetanus toxoid 30 days after a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers ***Safety*** To describe the safety profile of a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers
Endpoints:	***Immunogenicity*** 1) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA: a) At D0 (baseline) and D30 in toddlers after having received a single dose of either MenACYW conjugate vaccine or Nimenrix®, as part of study MET54 b) At D0 (baseline) in children before receiving a booster dose of MenACYW conjugate vaccine as part of study MET62 (3 years after having received a single dose of either MenACYW conjugate vaccine or Nimenrix®) 2) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA at D0 (baseline) and D30 after the administration of a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers Tetanus toxoid is contained as a carrier protein in both the investigational vaccine and the control vaccine that was used in study MET54. Therefore, blood samples will also be tested to assess: 3) Antibody concentrations against tetanus toxoid at D0 (baseline) and D30 after the administration of a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers ***Safety*** • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card [booklet or electronic device (e-diary)] and electronic case report book [CRB]) injection site reactions occurring up to 7 days after vaccination **Note**: The diary card may be either a booklet or an electronic device that contains an application to enter the information (e-diary). • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card [booklet or e-diary] and CRB) systemic reactions occurring up to 7 days after vaccination

	• Occurrence, nature (MedDRA PT), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to Visit 2 after vaccination • Occurrence, nature (MedDRA PT), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs, including AESIs, throughout the trial
Planned Sample Size:	A total of 188 subjects who participated in the MET54 study are planned to be enrolled.
Schedule of Study Procedures:	Vaccination All subjects will receive a single dose of MenACYW conjugate vaccine at Visit 1 (D0). Blood sampling All subjects will provide a pre-vaccination blood sample on D0 and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination at Visit 1). Collection of safety data • All subjects will be observed for 30 minutes after vaccination and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the CRB. • The subject's parent / legally acceptable representative will record information in a diary card (booklet or e-diary) about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to Visit 2. SAEs will be reported throughout the duration of the trial. • In addition, the subject's parent / legally acceptable representative will be asked to notify the site immediately about potential SAEs at any time during the trial. • Alerts will be sent to the e-diary (if applicable) and staff will contact the subject's parent / legally acceptable representative by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported, and to remind them to complete the diary card (booklet or e-diary) up to Visit 2 and to bring it back at Visit 2. • The completed diary card (booklet or e-diary) will be reviewed with the subject's parent / legally acceptable representative at Visit 2.
Duration of Participation in the Trial:	The duration of each subject's participation in the study will be 30 to 44 days.
Investigational Product:	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Form:	Liquid solution
Composition:	Each 0.5 milliliter (mL) dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients:

	Meningococcal capsular polysaccharides: Serogroup A ..... 10 micrograms (µg) Serogroup C ..... 10 µg Serogroup Y ..... 10 µg Serogroup W ..... 10 µg Tetanus toxoid protein carrier.....approximately 55 µg* * Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation.
Route:	IM
Batch Number:	To be determined
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) Participated in and completed (attended Visit 2) study MET54 2) Informed consent form has been signed and dated by the parent(s) or another legally acceptable representative (and by an independent witness, if required by local regulations) 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 where applicable
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) Participation in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure 2) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at a gap of at least 2 weeks before or after the study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. If the subject is due to receive vaccination(s) recommended for his / her age by the national immunization schedule at the time of the study, the subject will be recommended to complete his/her immunization schedule after Visit 2. 3) 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, Y, or W; or meningococcal B vaccine) <u>with the exception of the single dose of meningococcal vaccine administered as part of study MET54</u> 4) Receipt of immune globulins, blood or blood-derived products in the past 3 months 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 traveling 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 vaccine used in the trial or to a vaccine containing any of the same substances 9) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination in the Investigator's opinion 10) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination 11) Personal history of Guillain-Barré syndrome (GBS) 12) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine 13) Chronic illness 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 $\geq 38.0°C$). 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:	All immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set (FAS). All safety analyses will be performed on the Safety Analysis Set (SafAS). All analyses will be based on the overall study population as well as the type of meningococcal vaccine received in MET54 (subjects who received MenACYW conjugate vaccine and subjects who received Nimenrix® 3 years earlier as toddlers). ***Immunogenicity*** All analyses will be descriptive; no hypotheses will be tested. Descriptive statistics will be provided for the hSBA and rSBA antibody titers against meningococcal serogroups (A, C, Y, and W) and for antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine. In general, categorical variables will be summarized and presented by frequency counts, proportion percentages, and confidence intervals (CIs). The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For geometric mean titers (GMTs), 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

	Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups and the antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine. In summary, descriptive analyses on A, C, Y, and W serogroups will include but not be limited to: • hSBA and rSBA GMTs and 95% CI • hSBA and rSBA titer distribution and RCDC • Percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and 95% CI • Percentage of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 and 95% CI Percentage of subjects with hSBA and rSBA titer ≥4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with hSBA and rSBA vaccine seroresponse* rate and 95% CI ***hSBA vaccine seroresponse (definition proposed by the Center for Biologics Evaluation and Research [CBER] in 2016)** for serogroups A, C, Y, and W is defined as: • For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16. • For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer. **hSBA vaccine seroresponse (definition used in study MET54)** for serogroups A, C, Y, and W is defined as: • For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:8. • For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer **rSBA vaccine seroresponse** is defined as: • a post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or • a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8. In summary, descriptive analyses on anti-tetanus antibody concentrations will include but not be limited to: • Geometric mean concentrations (GMCs) and 95% CI • The percentage of subjects with antibody concentrations to tetanus toxoid ≥ 0.01 international units (IU)/mL and ≥ 0.1 IU/mL and 95% CI Data from MET54 and MET62 will also be combined and paired to evaluate antibody persistence and overall trends over 3 years. ***Safety*** Safety results will be described for subjects in the study. The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method). **Calculation of Sample Size:** This is an exploratory study with no hypothesis-driven primary objectives. All available subjects who participated in and completed the MET54 study and received either MenACYW conjugate vaccine or Nimenrix® vaccine, as a part of the study, will be enrolled.

Table of Study Procedures

Phase III Study, 2 Visits, 1 Vaccination, 2 Blood Samples, 1 Telephone Call, 30 Days Duration per Subject

Visit/Contact	**Visit 1**	**Telephone Call 1**	**Visit 2**
Trial timelines (days)	D0	D08	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*	X		
Review of temporary contraindications for blood sampling†			X
Allocation of subject number	X		
Blood sampling (BL), 5 mL‡	BL1		BL2
Vaccination§	X		
Immediate surveillance (30 minutes)	X		
Diary card (booklet or e-diary) provided	X		
Telephone call		X**	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited AEs	D0 to Visit 2		
Reporting of SAEs (including AESIs)††	To be reported throughout the study period		
Diary card (booklet or e-diary) reviewed and collected			X
Collection of reportable concomitant medications	X		X
Trial termination record			X

*Temperature needs to be measured and recorded in source documents.

† Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of the 30 to 44 day timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

‡ Blood sample at Visit 1 will be drawn before administration of vaccine

§ Subjects will receive 1 dose of MenACYW conjugate vaccine

** This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+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 (booklet or e-diary) up to Visit 2, to bring the diary card (booklet or e-diary) to the study center at Visit 2, and confirm the date and time of Visit 2. Additionally, an alert may be sent to the e-diary (as applicable) to remind the subject's parent / legally acceptable representative to report any SAEs, including AESIs, not yet reported and to continue to use the e-diary up to Visit 2, to bring the e-diary to the study center at Visit 2, and confirm the date and time of Visit 2.

†† AESIs will be collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

List of Abbreviations

µg	microgram(s)
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sampling/sample
CBER	Center for Biologics Evaluation and Research
CDM	Clinical Data Management
CFU	colony-forming unit
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
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
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	day
EDC	electronic data capture
ECL	electrochemiluminescent
EMA	European Medicines Agency
FAS	full analysis set
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
GPV	Global PharmacoVigilance
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G

IM	intramuscular(ly)
IMD	invasive meningococcal disease
IME	important medical event
IOM	Institute of Medicine
IRB	Institutional Review Board
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IU	international units
LLOQ	lower limit of quantitation
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
PS	polysaccharide
PT	preferred term
PV	Pharmacovigilance
RCDC	reverse cumulative distribution curve
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SMT	Safety Management Team
TMF	Trial Master File
ULOQ	upper limit of quantitation
UN	United Nations
WHO	World Health Organization

1 Introduction

1.1 Background

This study (MET62) will assess the immunogenicity and safety of a booster dose of the investigational quadrivalent Meningococcal Polysaccharide (serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) administered 3 years after a primary dose of MenACYW conjugate vaccine or Nimenrix® was administered to toddlers participating in the MET54 study. The persistence of the immune response against meningococcal serogroups A, C, Y, and W, 3 years after primary vaccination with either MenACYW conjugate vaccine or Nimenrix®, will also be described.

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

The epidemiology of *N meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. Meningococcal disease occurs worldwide in both endemic and epidemic forms with seasonal variation. In Europe, the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 19 year old group. The highest incidence rate in Europe is caused by serogroup B, followed by C (23). The highest proportion of meningococcal cases was due to serogroup B in the population under 5 years of age. The highest proportion of serogroup C cases was observed in the population 25 to 44 years of age while the proportion of serogroup Y cases was highest in the population aged 65 years and above. Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in 2013 - 2014 compared with an average of 1% to 2% of all IMD cases in earlier years (24). A gradual increase in serogroup Y IMD has also been recently

reported in Sweden during 2005 – 2012 (25) (26). Nearly 50% of all IMD was caused by serogroup Y in 2012 (25). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Scandinavian countries, accounting for 31% in Norway in 2009 - 2010 and 38% in Finland in 2010 (27).

The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, Y, and W in all age groups including children as young as 6 weeks of age, adolescents, and adults, including those 56 years of age and older.

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

The formulation has been evaluated in over 1639 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in completed studies MET39, MET44, MET50, and MET54. MenACYW conjugate vaccine is also being evaluated in ongoing Phase III studies (MET51 and MET57 in toddlers, MET35 in children (2 to 9 years of age), MET43 and MET56 in adolescents and adults, and MET49 in older adults ≥ 56 years of age). The relevant Phase II studies are discussed below.

MenACYW conjugate vaccine was found to be well tolerated and no unanticipated or new significant safety concerns have been identified in the clinical trials completed to date or in the ongoing MET56 study, where the MenACYW conjugate vaccine is administered to adolescents or adults who have received a dose of a meningococcal quadrivalent conjugate vaccine 4 to 10 years earlier.

1.2.1.1 Study MET39 (Phase II)

MET39 was a Phase II, randomized, open-label, multi-center study conducted in the US for which 580 healthy subjects from 2 to 15 months of age were enrolled. This study evaluated the optimal vaccination schedule in the infant/toddler population. Subjects in Group 1 through Group 4 received 1, 2, or 3 primary doses plus an additional dose of the MenACYW conjugate vaccine in the second year of life, concomitantly with routine pediatric vaccines at several different vaccination schedules. Subjects in Group 5 received 1 dose of the MenACYW conjugate vaccine concomitantly with routine pediatric vaccines. The routine pediatric vaccines given concomitantly with MenACYW conjugate vaccine at various schedules included Prevnar® or Prevnar 13 vaccine, Pentacel vaccine, ROTARIX® or RotaTeq vaccine, hepatitis B vaccine, M-M-RII vaccine, and VARIVAX vaccine.

Immunogenicity

After the primary series consisting of 1, 2, or 3 doses of MenACYW conjugate vaccine, protective serum bactericidal assay using human complement (hSBA) threshold titers of ≥ 1:8 were attained by > 88% of subjects for serogroup C and by 62% to 74% for serogroup A. For serogroups Y and

W, ≥ 90% achieved the threshold titer after 3 doses, 75% to 84% after 2 doses, but only 25% after a single dose administered at 6 months of age.

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

Safety

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

No deaths occurred within 30 days. There were 2 subjects in Group 4 who died during the study, 1 as a result of hypoxic ischemic encephalopathy which started 96 days after the 6-month vaccination and 1 as a result of non-accidental head trauma 36 days after the 12-month vaccination. These events were considered by the Investigator as unrelated to study vaccine. There were 2 other subjects who discontinued the study due to a serious adverse event (SAE) and the receipt of intravenous immunoglobulin treatment: 1 subject in Group 2 with Kawasaki disease, 106 days after the 6-month vaccination; and 1 subject in Group 3 with middle lobe pneumonia and Kawasaki disease, 50 and 52 days, respectively, after the 4-month vaccinations. One other subject in Group 4 was discontinued due to a non-serious adverse event (AE) (viral rash 1 day after the 6-month vaccinations). None of these AEs leading to discontinuation were considered by the Investigator as related to the vaccine. There were no related SAEs during this study.

1.2.1.2 Study MET54 (Phase II)

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

Immunogenicity

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

1.3 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.

In addition, data generated for Nimenrix® (Meningococcal group A, C, W-135, and Y conjugate vaccine) showed that booster vaccination of children who had previously received 1 dose of MenACWY-TT or MenC conjugate vaccine (MenC-CRM197) at 12–23 months, induced robust immune responses for all serogroups with an acceptable safety profile (28).

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.

As with any vaccine, MenACYW conjugate vaccine may not protect 100% of individuals against the disease it is designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine may cause injection site reactions such as pain, swelling, and erythema, or certain systemic events such as fever, headache, malaise, and myalgia. 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 that are not yet known.

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

Guillain-Barré syndrome (GBS) has been reported mostly in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of a US licensed meningococcal conjugate vaccine (29). 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 (30).

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

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

The risk of vasovagal syncope exists after any vaccination in the adolescent age group, although it has not been specifically reported in the age group under study as part of this protocol (34). A few cases of immediate vasovagal-like response or syncope have been observed in adolescent subjects who had received MenACYW conjugate vaccine.

The potential risks associated with blood drawing include local pain, bruising, and, rarely, fainting. Infection at the site of needle insertion could theoretically occur but is exceedingly rare when the standard sterile technique is utilized.

The potential risk listed here are not exhaustive. Refer to the Investigator's Brochure of the investigational vaccine for additional information regarding the potential risks.

1.4 Rationale for the Study

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

Meningococcal polysaccharide vaccines have two important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) polysaccharides alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of polysaccharide vaccines in infants and children has been shown to be improved by conjugating the polysaccharides to protein carriers. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of polysaccharide-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET39 and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials.

The purpose of MET62 is to describe the immune persistence of the priming dose and describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine in children in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix® as part of the MET54 study.

2 Study Objectives

Immunogenicity

1) To describe the antibody persistence of meningococcal serogroups A, C, Y, and W before a booster dose in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

2) To describe the antibody responses to meningococcal serogroups A, C, Y, and W 30 days after a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers
3) To describe the antibody responses against tetanus toxoid 30 days after a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

Safety

To describe the safety profile of a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers.

The immunogenicity and safety endpoints for the objectives are presented in Section 9.1.1 and Section 9.2.2, respectively.

3 Investigators and Study Organization

This study will be conducted in approximately 8 centers in Finland. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator. Details of the study centers, the Investigators at each center, and the Coordinating Investigator are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal Safety Management Team (SMT) will perform a safety analysis on safety data after vaccination.

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 (IEC) or Institutional Review Board (IRB).

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

The Investigator will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All 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, open-label, multi-center study to describe the immune persistence of the priming dose and describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine in children in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix® as part of the MET54 study.

Subjects who were vaccinated 3 years (± 45 days) earlier at 12 to 23 months of age in study MET54 will be eligible for enrollment in study MET62.

All subjects will receive a single dose of MenACYW conjugate vaccine on Day (D) 0.

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

Solicited AE information will be collected for 7 days after vaccination; unsolicited AE information will be collected from Visit 1 (D0) to Visit 2 (D30 [+14 days]), and SAE information (including adverse events of special interest [AESIs]) will be collected throughout the study period.

5.1.2 Justification of the Study Design

[redacted] MET62 is a study that will be conducted as part of the Phase III development of MenACYW conjugate vaccine in which the vaccine candidate will be evaluated as a booster dose in children. This study will describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine given 3 years after a primary dose of MenACYW conjugate vaccine or Nimenrix® was administered to toddlers. This study will also describe the antibody persistence 3 years after primary vaccination prior to administration of the booster dose. Subjects who were included in study MET54 are eligible to be enrolled in MET62.

Since all subjects will receive MenACYW conjugate vaccine; this study has been proposed as an open-label study. Since MenACYW conjugate vaccine has been evaluated in infants, toddlers, and adults without raising any safety concerns, safety assessment will be done up to 30 days after vaccination.

5.1.3 Study Plan

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

Vaccination

All subjects will receive a single dose of MenACYW conjugate vaccine at Visit 1 (D0).

Blood Sampling

All subjects will provide a pre-vaccination blood sample on D0 and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination at Visit 1).

Collection of Safety Data

- All subjects will be observed for 30 minutes after vaccination and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the electronic case report form (CRF) (see Section 9.2.3.1).
- The subject's parent / legally acceptable representative will record information in a diary card (booklet or electronic device [e-diary]) about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to Visit 2. SAEs will be reported throughout the duration of the trial.
- In addition, the subject's parent / legally acceptable representative will be asked to notify the site immediately about potential SAEs at any time during the trial.
- Alerts will be sent to the e-diary (if applicable) and staff will contact the subject's parent / legally acceptable representative by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported, and to remind them to complete the diary card (booklet or e-diary) up to Visit 2 and to bring it back at Visit 2.
- The completed diary card (booklet or e-diary) will be reviewed with the subject's parent / legally acceptable representative at Visit 2.

Note: The diary card may be either a booklet or an electronic device that contains an application to enter the information (e-diary).

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.

Visit 1 (D0): Inclusion, Randomization, Blood Sample, and Vaccination

1) Give the subject's parent / legally acceptable representative information about the trial, answer any questions, obtain written informed consent and give the subject's parent / guardian a signed copy of the ICF.
2) Check inclusion and exclusion criteria for eligibility (see Section 5.2.4 and Section 5.2.5, respectively).
3) Collect relevant demographic information.
4) Obtain verbal medical history about the subject since participation in MET54.

5) Conduct a history-directed physical examination, including temperature (a physical examination conducted during the same day as part of routine clinical care may be used for this purpose).
6) Call the interactive response technology (IRT) system for assignment of subject number.
7) Obtain the first blood sample (5 milliliter [mL]) (see Section 7 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (no more than 3 attempts), then Visit 1 can be rescheduled to a later date at which point informed consent and inclusion/exclusion criteria must be re-validated.[a] If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.
8) Administer MenACYW conjugate vaccine to the subject in the deltoid muscle. The vaccine must be administered on the side opposite to that of the blood sampling.
9) Observe the subject for 30 minutes, and record any AE in the source document.
10) Give the subject's parent / legally acceptable representative a diary card (booklet or e-diary), a thermometer, and a ruler, and go over the instructions for their use.
11) Remind the subject's parent / legally acceptable representative to expect a telephone call 8 days after Visit 1 and to bring back the diary card (booklet or e-diary) when they return for Visit 2 at a specified date and time.
12) Remind the subject's parent / legally acceptable representative to notify the site in case of an SAE.
13) Complete the relevant CRFs for this visit.

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

Note: If D08 falls on a weekend or a holiday, the telephone call may be made on the following business day. If the subject's parent / legally acceptable representative is not available, the study staff should document the attempts to make contact.

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

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

An alert may also be sent to the e-diary (as applicable) to remind the subject's parent / legally acceptable representative to report any SAEs, including AESIs, not yet reported and to continue to use the e-diary up to Visit 2, to bring the e-diary to the study center at Visit 2, and confirm the date and time of Visit 2.

Visit 2 (D30 [+14 days] after Visit 1): Collection of Safety Information and Blood Sample

1) Review the pages / fields of the diary card (booklet or e-diary) with the subject's parent / legally acceptable representative, including any AEs, medications, or therapy that occurred since vaccination.

2) Review the temporary contraindications for blood sampling (see Section 5.2.8).

3) Obtain the second blood sample (see Section 7 for detailed instructions regarding the handling of blood samples).

4) Complete the relevant CRFs for this visit (including the termination record).

5) If the subject's parent / legally acceptable representative does not return for Visit 2, and the diary card booklet is not received at the site, or the e-diary data has not been completed / received at the site, site personnel will contact the subject's parent / legally acceptable representative by telephone. During the telephone call, the subject's parent / legally acceptable representative will be reminded to return the diary card (booklet or e-diary) to the study site. Telephone calls will be documented on the Telephone / Interview Record. If the study personnel are unable to contact the subject's parent / 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/Vaccination Discontinuation:

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

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

5.1.5 Planned Study Calendar

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

Planned subject participation - FVFS (first visit, first subject) to
LCLS (last contact, last subject): 14 February 2018 to 16 October 2018

Planned inclusion period - FVFS to FVLS (first visit, last subject)[a]:	14 February 2018 to 31 August 2018
Planned primary vaccination period:	14 February 2018 to 31 August 2018
Planned end of study:	16 October 2018
Planned date of final clinical study report:	26 September 2019

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Before the start of the trial, the Investigator and / or study staff will contact the parents / legally acceptable representatives of subjects who had previously participated in study MET54 and invite them to participate in the study. The site will ensure that any advertisements used to recruit subjects (e.g. letters, pamphlets, and posters) are submitted to Sanofi Pasteur for review prior to submission to the IEC/ IRB for approval.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject and / or a subject's parent or appropriate and legally acceptable representative voluntarily confirms his or her willingness to participate / allow the child 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 parent / 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.

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

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

If new information becomes available that may be relevant to the parent's / legally acceptable representative's willingness to continue participation in the study, this will be communicated to

[a] Enrollment can be achieved from the 3-year anniversary (±45 days) of the FVFS in study MET54 to the 3-year anniversary (±45 days) of the FVLS in MET54.

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:

MET62 is a study to be conducted in children approximately 4 to 5 years of age to obtain safety and immunogenicity data (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 (e.g., collection of blood sample). 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.

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) Participated in and completed (attended Visit 2) study MET54
2) Informed consent form has been signed and dated by the parent(s) or another legally acceptable representative (and by an independent witness, if required by local regulations)
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 where applicable

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 preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
2) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at a gap of at least 2 weeks before or after the study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. If the subject is due to receive vaccination(s) recommended for his / her age by the national

immunization schedule at the time of the study, the subject will be recommended to complete his/her immunization schedule after Visit 2.

3) 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, Y, or W; or meningococcal B vaccine) with the exception of the single dose of meningococcal vaccine administered as part of study MET54
4) Receipt of immune globulins, blood or blood-derived products in the past 3 months
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 traveling 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 vaccine used in the trial or to a vaccine containing any of the same substances[a]
9) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination in the Investigator's opinion
10) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination
11) Personal history of Guillain-Barré syndrome (GBS)
12) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine
13) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[b]
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.

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

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

16) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

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

5.2.6 Medical History

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

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

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

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

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

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable.

5.2.8 Contraindications for Subsequent Blood Draw

Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this 30 to 44 day timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.9 Conditions for Withdrawal

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 permission (withdrawal)
- At the request of the subject's parent / legally acceptable representative (dropout)

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

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

Withdrawn subjects will not be replaced.

5.2.10 Lost to Follow-up Procedures

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

5.2.11 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.2.1.
Lost to Follow-up	To be used when the subject's parent / legally acceptable representative cannot be found or contacted in spite of efforts to locate him/her before the date of his/her child's 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 bring the child to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (e.g., deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine / treatment administration). • The subject or the parent/legally acceptable representative signed the certified letter sent by the investigator but did not give any other news and did not bring the child to the following visit.
Withdrawal by Parent / Legally Acceptable Representative	To be used: • When the subject's parent / legally acceptable representative indicated unwillingness to allow his/her child to continue in the study • When the subject's parent / legally acceptable representative made the decision to discontinue his/her child's participation in the study for any personal reason other than an SAE/AE (e.g., subject is relocating, inform consent withdrawal, etc.)

5.2.12 Follow-up of Discontinuations

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

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

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

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on a study related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or

back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

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

5.4 Modification of the Study and Protocol

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

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs / IRBs may be notified of administrative changes and will provide approval according to local regulations.

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

5.5 Interruption of the Study

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

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

6 Vaccines Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product

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

Form: Liquid solution

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.1.1.1 Composition

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

Meningococcal capsular polysaccharides:

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

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

6.1.1.2 Preparation and Administration

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

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

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

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 in the deltoid muscle of the arm. After vaccine administration, the used syringe and needle will be disposed of in accordance with currently established guidelines.

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

6.1.1.3 Dose Selection and Timing

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

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

6.1.2 Identity of Control Product

Not applicable.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

MenACYW conjugate vaccine will be supplied in single-dose vials, labeled and packaged 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 (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

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

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

6.3.2.3 Product Accountability

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

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

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

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

6.3.3 Replacement Doses

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

6.3.4 Disposal of Unused Products

Unused or wasted products will be 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 Investigators will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

The study is open label and all subjects will receive MenACYW conjugate vaccine; there is no need for code-breaking procedures.

6.5 Randomization and Allocation Procedures

Subjects will not be randomized.

On the day of enrollment, a subject whose parent/legally acceptable representative signs the ICF will be assigned a subject number.

Site staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data in response to IRT system prompts.

Subject numbers that are assigned by the IRT system will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example, Subject 840000100005 is the fifth subject enrolled in Center Number 1 in the US (840 being the US country code).

Subject numbers should not be reassigned for any reason.

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 given to each subject, and the disposal of unused or wasted doses

6.7 Concomitant Medications and Other Therapies

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

Documentation in the CRB of 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 the CRB will be restricted to only 3 days (72 hours) prior to each blood sampling time point.

Collection Period in Source Documents

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

Categories of Reportable Medications and Reporting Period

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

- 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.

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

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

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

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

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

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

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

Dosage and administration route and 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 in response to an AE will be captured in the "Action Taken" section of the AE CRB only. No details will be recorded in the concomitant medication CRB unless the medication(s) received belongs to one of the prelisted categories.

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

7 Management of Samples

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

7.1 Sample Collection

At Visits 1 and 2, 5 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity; will write the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 Sample Preparation

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

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

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

The subject's number and the date of sampling, the number of aliquots obtained, the date and time of preparation, and the parent's / legally acceptable representative's consent for future use of his / her child's 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 laboratory will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

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

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 (booklets or e-diaries), 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 Clinical Logistics Coordinator and/or Service Provider, indicating the quantity required. Contact information is provided in the Operating Guidelines.

9 Endpoints and Assessment Methods

9.1 Immunogenicity

9.1.1 Immunogenicity Endpoints

The endpoints for the evaluation of immunogenicity are:

1) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA:
   a) At D0 (baseline) and D30 in toddlers after having received a single dose of either MenACYW conjugate vaccine or Nimenrix®, as part of study MET54
   b) At D0 (baseline) in children before receiving a booster dose of MenACYW conjugate vaccine as part of study MET62 (3 years after having received a single dose of either MenACYW conjugate vaccine or Nimenrix®)
2) Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA at D0 (baseline) and D30 after the administration of a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

Tetanus toxoid is contained as a carrier protein in both the investigational vaccine and the control vaccine that was used in study MET54. Therefore, blood samples will also be tested to assess:

3) Antibody concentrations against tetanus toxoid at D0 (baseline) and D30 after the administration of a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

9.1.2 Immunogenicity Assessment Methods

[redacted]

9.2 Safety

9.2.1 Safety Definitions

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

Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

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

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

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

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

Adverse Reaction (AR):

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

(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) prelisted in the protocol and CRB (e.g., injection site pain or headache occurring between D0 and D07 post-vaccination).

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

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

The assessment of these reactions by the investigator is mandatory.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D07 is a solicited reaction (i.e., prelisted in the protocol and CRB), then a headache starting on D07 is a solicited reaction, whereas headache starting on D08 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 (e.g., erythema that is localized but that is not occurring at the injection site).

Adverse Event of Special Interest (AESI):

An adverse event of special interest 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 (e.g., regulators) might also be warranted.

9.2.2 Safety Endpoints

The endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card [booklet or e-diary] and CRB) injection site reactions occurring up to 7 days after vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card [booklet or e-diary] and CRB) systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA PT), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to Visit 2 after vaccination.
- Occurrence, nature (MedDRA PT), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs, including AESIs, throughout the trial.

9.2.3 Safety Assessment Methods

At Visit 2, the Investigator or a delegate will ask the subject's parent / legally acceptable representative about any solicited reactions and unsolicited AEs recorded in the diary card (booklet or e-diary), 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.

9.2.3.1 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.

9.2.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 07 After Vaccination)

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

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

  The action(s) taken by the subject's parent / legally acceptable representative to treat and/or manage any **solicited reactions** will be classified in the CRB using the following list (all applicable items should be checked):
  - None
  - Medication
  - Health care provider contact
  - Hospitalized

Subjects' parents / legally acceptable representatives will be contacted by telephone 8 days after vaccination to remind them to record all safety information in the diary card (booklet or e-diary).

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

Table 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards (booklets or e-diaries) and CRB, together with the intensity scales.

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

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

* For the subjective reaction of pain, parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card (booklet or e-diary). 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 LLT)	**Fever**	**Headache**	**Malaise**	**Myalgia**
MedDRA PT	Pyrexia	Headache	Malaise	Myalgia
Diary card (booklet or e-diary) term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥ 38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

CRB term (MedDRA LLT)	**Fever**	**Headache**	**Malaise**	**Myalgia**
MedDRA PT	Pyrexia	Headache	Malaise	Myalgia
Diary card (booklet or e-diary) term	Temperature	Headache	Feeling unwell	Muscle aches and pains
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

* For all reactions but fever, parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card (booklet or e-diary). 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:

Parents / legally acceptable representatives are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card (booklet or e-diary) 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.

9.2.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, parents / legally acceptable representatives will be instructed to record any other medical events that may occur during the 30-day period after vaccination. Space will be provided in the diary card (booklet or e-diary) for this purpose.

Information on SAEs will be collected and assessed throughout the study, from the time of vaccination until 30 days (+14 days) after vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). 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 AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

[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 AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.2.3.5.

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

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

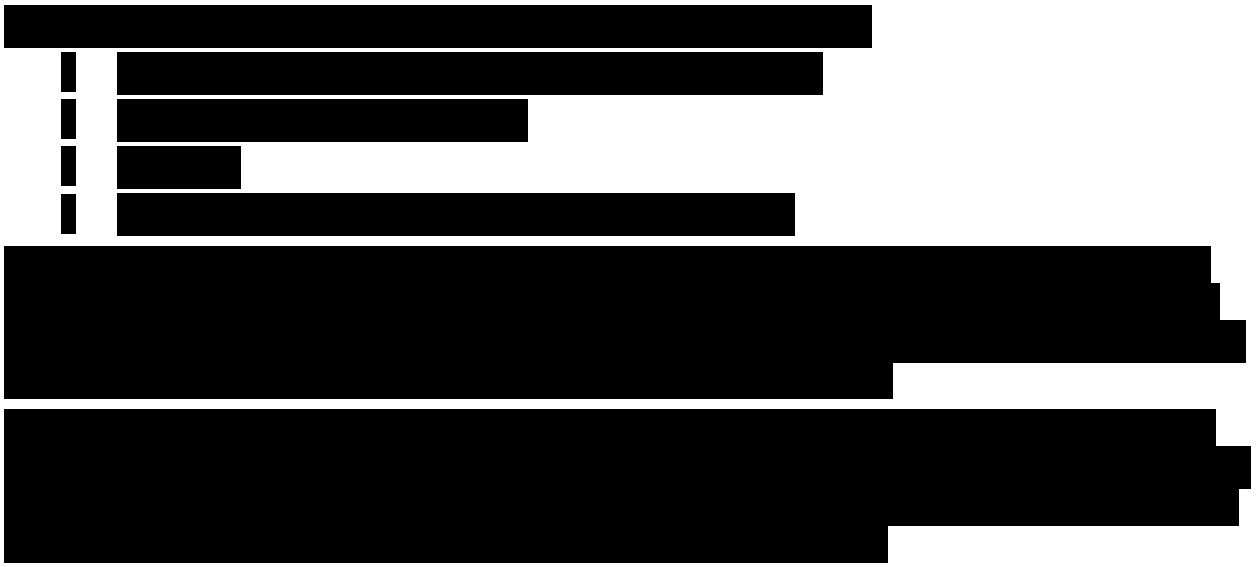
  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- 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

9.2.3.4 Adverse Events of Special Interest



9.2.3.5 Assessment of Causality

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

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

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

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

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

9.3 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. It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

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

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

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

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

- By fax, to the following number: [redacted]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted] (see the Operating Guidelines for directions on how to send a password protected email)
- By express mail, to the following address: Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global PharmacoVigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370, USA

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

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

10.2 Follow-up Reporting by the Investigator

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

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

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

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

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.2.3.5.

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

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

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

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

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

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards (booklets or e-diaries), specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants' parents / legally acceptable representatives for the recording of daily safety information as described in Section 9.2.3. These diary cards (booklets or e-diaries) will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Parents / legally acceptable representatives will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct parents / legally acceptable representatives on how to correctly use these tools.

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 (booklet or e-diary), and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. Data from the e-diary will be integrated into the CRB. (Any information that was not documented in the diary card [booklet or e-diary] 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 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 PV Global Safety Expert and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

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

Management of Clinical and Laboratory Data

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

During the study, clinical data reported in the CRB 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. 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. A statistical analysis plan (SAP) will be written and peer reviewed before any analyses. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

12.1.1 Hypotheses and Statistical Methods for the Objective

12.1.1.1 Hypotheses

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

12.1.1.2 Statistical Methods

Immunogenicity

Descriptive statistics will be provided for the hSBA and rSBA antibody titers against meningococcal serogroups (A, C, Y, and W) and for antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine.

In general, categorical variables will be summarized and presented by frequency counts, proportion percentages, and confidence intervals (CIs). The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages (43). For geometric mean titers (GMTs), 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups or antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine.

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

- hSBA and rSBA GMTs and 95% CI

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

In summary, descriptive analyses on anti-tetanus antibody concentrations will include but not be limited to:

- Geometric mean concentrations (GMCs) and 95% CI
- The percentage of subjects with antibody concentrations to tetanus toxoid ≥ 0.IU/mL and ≥ 0.1 IU/mL and 95% CI

Data from MET54 and MET62 will also be combined and paired to evaluate antibody persistence and overall trend over 3 years.

Safety

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

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

Unsolicited AEs will be collected, coded, and summarized by MedDRA system organ class and PT. For each unsolicited AE, the number of subjects with at least one instance of that event will

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[a] **hSBA vaccine seroresponse (definition proposed by the Center for Biologics Evaluation and Research [CBER] in 2016)** for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

hSBA vaccine seroresponse (definition used in study MET54) for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:8.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

rSBA vaccine seroresponse is defined as:

- a post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8,

or

- a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8.

be reported. Unsolicited AEs will also be tabulated by intensity and relatedness of study vaccine and by other categories specified in the endpoints.

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

12.2 Analysis Sets

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

12.2.1 Full Analysis Set

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

12.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one dose of the study vaccine[a] and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received.

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

12.2.3 Per-Protocol Analysis Set

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

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

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

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

In the event of a local or national immunization program with a pandemic influenza vaccine, subjects who receive 1 or more doses of a pandemic influenza vaccine at any time during the study will not be withdrawn from the study.

12.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS. All safety analyses will be performed on the SafAS. All analyses will be based on the overall study population as well as the type of meningococcal vaccine received in MET54 (subjects who received MenACYW conjugate vaccine and subjects who received Nimenrix® 3 years earlier as toddlers).

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

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

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

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

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

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

12.4 Interim / Preliminary Analysis

No preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

This is an exploratory study with no hypothesis-driven primary objectives. All available subjects who participated in and completed the MET54 study and received either MenACYW conjugate vaccine or Nimenrix® vaccine, as a part of the study, will be enrolled.

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 (booklets or e-diaries), medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a diary card (booklet), the study coordinator will obtain verbal clarification from the subject, enter the response into the "investigator's comment" page of the diary card (booklet), and transfer the information to the CRB. For missing or discrepant data on a diary card (e-diary), the study site staff will obtain verbal clarification from the subject, enter the response in the source document, and transfer the information to the CRB.

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

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

[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.

If an e-diary is used in this trial, the e-diary data, which has been integrated into the CRB, will be available on the vendor's web-based portal for review. At the end of the trial, data in the web-based portal will be stored and then will later be destroyed according to local regulation.

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

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

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

- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the 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 must keep all study documents after the completion or discontinuation of the study, whatever the nature of the investigational center (private practice, hospital, or institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, study documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any study documents upon less than 90 days advance written notification to the Sponsor. In addition, study documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the study documents.

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

13.5 Financial Contract and Insurance Coverage

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

13.6 Stipends for Participation

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

13.7 Publication Policy

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

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

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

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15 Signature Page

Sponsor Signature

I confirm that this protocol (version 2.0 dated 15 March 2018) is in accordance with applicable regulations and Good Clinical Practice.

Function	Name	Date	Signature
Sponsor's Responsible Medical Officer [redacted] Sanofi Pasteur	[redacted]	03/16/2018	[redacted]