NCT Number: NCT02842866

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adults Age 56 Years and Older

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® – A/C/Y/W-135 in adults ≥ 56 years of age in the United States.

Clinical Trial Protocol, Amendment 1

Health Authority File Number(s):	BB-IND #: 14171
WHO Universal Trial Number (UTN):	U1111-1124-7760
Trial Code:	MET49
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid Solution / Intramuscular (IM)
Indication For This Study:	MenACYW conjugate vaccine as a single dose for adults 56 years of age and older
Manufacturer:	Same as Sponsor
Coordinating Investigator:	[redacted]
Sponsor's Responsible Medical Officer:	[redacted], Sanofi Pasteur Inc. Tel: [redacted] Fax:
Product Safety Officer:	[redacted], Sanofi Pasteur Inc. Tel: [redacted] Fax:
Clinical Trial Manager:	[redacted], Sanofi Pasteur Inc. Tel: [redacted]
Version and Date of the Protocol:	Version 3.0 dated 20 May 2016

This protocol version 3.0 is the first amendment to the initial trial protocol version 2.0, dated 22 December 2015.

Table of Contents

List of Tables

Synopsis

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

Title of the Trial:	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adults Age 56 Years and Older
Development Phase:	Phase III
Coordinating Investigator:	[redacted]
Trial Centers:	This will be a multi-center trial conducted at approximately 35 sites in the United States. Investigators and sites will be listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	3Q 2016 to 2Q 2017
Trial Design and Methodology:	This will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® - A/C/Y/W-135 in adults ≥ 56 years of age in the US. Approximately 900 healthy adults will be randomized in a 1:1 ratio to the following groups: • Group 1: MenACYW conjugate vaccine • Group 2: Menomune® - A/C/Y/W-135 Enrollment will be stratified by age (see Table S1). For subjects 56 to 64 years of age, 200 subjects will be enrolled in both Group 1 and Group 2. For subjects 65 years of age and older, 250 subjects will be enrolled in both Group 1 and Group 2. These subjects will be further stratified into 2 groups as 65 to 74 years of age and 75 years and older. At least 25% of the 250 subjects will be enrolled in each of these age groups.

	Table S1: Testing strategy for *N. meningitidis* serogroups ACYW **ACYW serogroups tested by hSBA* (all subjects)** / **ACYW serogroups tested by rSBA† (subset)** **Group 1** **56-64 years**: 200 / 50 **≥ 65 years:**: 250 / 50 **65-74 years**: 70-180 / 15-35 **≥ 75 years**: 70-180 / 15-35 **Group 2** **56-64 years**: 200 / 50 **≥ 65 years:**: 250 / 50 **65-74 years**: 70-180 / 15-35 **≥ 75 years**: 70-180 / 15-35 * hSBA: serum bactericidal assay using human complement † rSBA: serum bactericidal assay using baby rabbit complement All subjects will provide pre-vaccination blood samples for immunogenicity assessment at baseline (Visit 1) and at Day (D)30 (+14-day window) post-vaccination (Visit 2). Solicited adverse event (AE) information will be collected for 7 days after vaccination, unsolicited AE information will be collected from Visit 1 to D30 (Visit 2), and serious adverse event (SAE) information will be collected from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAAEs) will be collected from Visit 1 through Visit 2 (as part of the collection of unsolicited AE information) and from Visit 2 through D180 (+14 days) (as MAAEs).
Early Safety Data Review:	This trial will not include an early review of safety data (i.e., no early safety review[s] of preliminary safety data occurring at pre-determined milestones defined in the protocol with pause in enrollment.) However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), or the governing regulatory authorities in the country where the trial is taking place. If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the trial subjects and should assure appropriate therapy and follow-up.
Primary Objectives:	To demonstrate the non-inferiority of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine compared to those observed following the administration of a single dose of Menomune® – A/C/Y/W-135.
Primary Endpoints:	Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at baseline (D0, before vaccination) and 30 days after vaccination
Secondary Objectives:	1) To compare the hSBA antibody geometric mean titers (GMTs) of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine to those observed following the administration of Menomune® – A/C/Y/W-135

Secondary Endpoints:	1) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine and Menomune® – A/C/Y/W-135
Observational Objectives:	***Immunogenicity*** • To describe antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 • To describe antibody titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using baby rabbit complement (rSBA) at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 in a subset of 100 subjects per treatment group. ***Safety*** To describe the safety profile of MenACYW conjugated vaccine compared to that of the licensed Menomune® – A/C/Y/W-135 after a single administration.
Observational Endpoints:	***Immunogenicity*** Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 ***Safety*** • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination. • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card (DC) and electronic case report form [CRF]) injection site reactions occurring up to 7 days after vaccination. • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's DC and CRF) systemic reactions occurring up to 7 days after vaccination. • Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs occurring up to Visit 2. • Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the trial. • Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness, relationship to vaccination, and outcome for MAAEs from Visit 2 to the 6-month follow-up contact. MAAEs will be collected as unsolicited AEs up to Visit 2.
Planned Sample Size:	A total of 900 subjects are planned to be enrolled: • Group 1 (MenACYW conjugate vaccine): planned = 450; evaluable = 382 • Group 2 (Menomune® – A/C/Y/W-135): planned = 450; evaluable = 382

Schedule of Study Procedures:	Vaccination All subjects will receive a single dose of either MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 at Visit 1 (D0). Blood sampling All subjects will provide a pre-vaccination blood sample at Visit 1 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 CRF. • The subject will record information in a DC 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. • The subject will record information about any possible SAEs and MAAEs in a memory aid (MA) from Visit 2 until the 6 month (+14 days) telephone call. • In addition, the subject will be asked to notify the site immediately about any potential SAEs at any time during the trial. • Staff will contact the subject by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the DC up to Visit 2 and to bring it back to Visit 2. • The completed DC will be reviewed with the subject at Visit 2. • Staff will contact the subject by telephone at 6 months (+14 days) after vaccination to review the MA and identify the occurrence of any MAAEs, as well as SAEs that have not been reported.
Duration of Participation in the Trial:	The duration of each subject's participation in the trial will be 180 to 194 days. There will be a safety follow-up telephone call 6 months (+14 days) after vaccination.
Investigational Product:	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Form:	Liquid Solution
Composition:	Each 0.5 milliliter (mL) dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients: Meningococcal capsular polysaccharides: Serogroup A ..... 10 micrograms (µg) Serogroup C.....10 µg Serogroup Y .....10 µg Serogroup W.....10 µg Tetanus toxoid protein carrier ..... approximately 65 µg
Route:	Intramuscular (IM)
Batch Number:	To be determined

Control Product:	**Menomune® – A/C/Y/W-135:** (Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W-135 Combined) (Sanofi Pasteur, Inc., Swiftwater, PA, USA)
Form:	Lyophilized single-dose vial with 0.6-mL vial of diluent (sterile, pyrogen-free distilled water without preservatives)
Composition:	After reconstitution with diluent as indicated in the Prescribing Information, each 0.5mL dose contains 50 µg of group-specific polysaccharide antigens from each of Groups A, C, Y and W-135 in an isotonic sodium chloride solution. Each dose of vaccine also contains 2.5 to 5 milligram (mg) of lactose as a stabilizer.
Route:	Subcutaneous
Batch Number:	To be determined (Provided by Sponsor))
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) Age ≥ 56 years on the day of inclusion 2) Informed consent form has been signed and dated 3) Able to attend all scheduled visits and to comply with all trial procedures
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination) 2) 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 3) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after study vaccine. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. 4) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B vaccine) 5) Receipt of immune globulins, blood or blood-derived products in the past 3 months 6) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

	7) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically 8) At high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease) 9) Known systemic hypersensitivity to latex or 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 10) Personal history of Guillain-Barré syndrome (GBS) 11) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within at least 10 years of the proposed study vaccination 12) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination, in the Investigator's opinion 13) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion 14) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily 15) Current alcohol abuse or drug addiction 16) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion 17) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature $\geq$ 100.4°F). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided 18) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 19) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
Statistical Methods:	All immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set (FAS) according to randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS). Subjects will be analyzed according to the vaccine they actually received. **Primary Objective** Thirty days after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 , the percentages of subjects who achieve an hSBA vaccine seroresponse* for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2. Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$ Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$ where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected.

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

* hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

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

Secondary Objectives

Thirty days after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135, the hSBA geometric mean titer ratio (GMTR) between Group 1 and Group 2 will be calculated and 95% CI will be provided.

Observational Objectives

Immunogenicity

Descriptive statistics will be provided for the hSBA and rSBA* antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menomune® – A/C/Y/W-135. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

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

Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menomune® – A/C/Y/W-135 treatment groups.

Safety

Safety results will be described for subjects in both study groups. The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method).

Calculation of Sample Size:

A total of 900 subjects will be enrolled.

[redacted]

Table of Study Procedures

Phase III Trial, 2 Visits, 1 Vaccination, 2 Blood Samples, 2 Telephone Calls,
180 Days' Duration per Subject

Visit/Contact	**Visit 1**	**Telephone Call 1**	**Visit 2**	**Telephone Call 2**
Trial timelines (days)	D0	D08	D30	D180
Time windows (days)	--	+2 days	+14 days	+14 days
Informed consent form	X			
Inclusion/exclusion criteria	X			
Collection of demographic data	X			
Urine pregnancy test (if applicable)	X			
Medical history	X			
Physical examination*	X			
Review of temporary contraindications for blood sampling†			X	
Randomization/allocation of subject number	X			
Blood sampling (BL) 10 mL‡	BL1		BL2	
Vaccination§	X			
Immediate surveillance (30 minutes)	X			
DC provided	X			
Telephone call		X**		X††
Recording of solicited injection site and systemic reactions	D0 to D07			
Recording of unsolicited AEs	Visit 1 through Visit 2			
DC reviewed and collected			X	
Recording of MAAEs‡‡			After Visit 2 to Telephone Call 2	
Reporting of SAEs	To be reported throughout the study period			
Collection of reportable concomitant medications	X		X	
MA provided§§			X	
Termination of active phase of trial			X	
Completion of 6-month follow-up				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 Visit 1). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

‡ A pre-vaccination blood sample will be collected from all subjects at D0.

§ Subjects will receive 1 dose of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135.

** This call is made 8 to10 days after the vaccinations on D0. 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 not yet reported, and will remind the subject to continue using the DC up to Visit 2, to bring the DC to the study center at Visit 2, and confirm the date and time of Visit 2.

†† Staff will contact the subject by telephone at 6 months (180 days + 14 days) after D0 vaccination to identify the occurrence of any MAAEs or SAEs not yet reported.

‡‡ MAAEs that occur between the Visit 1 (D0) and Visit 2 will be recorded as unsolicited AEs.

§§The MA is used for the recording of SAEs and MAAEs. The site staff will make a telephone call to the subject to obtain the information 180 days (+ 14 days) after the vaccinations on D0. Since the timeframe between Visit 1 and Visit 2 (inclusive) will be captured in the DC, the MA will be used to collect SAE and MAAE data from Visit 2 to Telephone Call 2.

List of Abbreviations

µg	microgram
AE	adverse event
AR	adverse reaction
BL	blood sample(ing)
CDM	Clinical Data Management
CFU	colony-forming unit
CI	confidence interval
C&MQO	Clinical and Medical Quality Operations
CRA	Clinical Research Associate
CRF	case report form (electronic)
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	day
DC	diary card
EDC	electronic data capture
eSAE	electronic Serious Adverse Event (Form)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMT	geometric mean titer
GPV	Global PharmacoVigilance
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IMD	invasive meningococcal disease
IND	investigational new drug (application)
IOM	Institute of Medicine

IRB	Institutional Review Board
IWRS	interactive web response system
LCLS	last contact, last subject
LLT	lowest level term
LLOQ	lower limit of quantitation
MA	memory aid
MAAE	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
NSAID	non-steroidal anti-inflammatory drug
PPAS	Per-Protocol Analysis Set
PS	polysaccharides
PSO	Product Safety Officer
R&D	Research and Development
RCDC	reverse cumulative distribution curve
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	statistical analysis plan
SMT	Safety Management Team
TMF	trial master file
UAR	unexpected adverse reaction
ULOQ	upper limit of quantitation
UTN	Universal Trial Number
WHO	World Health Organization

1 Introduction

1.1 Background

This is a trial using MenACYW conjugate vaccine against invasive meningococcal disease. This Phase III trial will evaluate the immunogenicity and safety of a single dose of the quadrivalent Meningococcal Polysaccharide (Serogroups A, C, Y and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in adults 56 years of age and older. The purpose of MET49 is to demonstrate non-inferiority of immunogenicity and evaluate the safety of a single dose of MenACYW conjugate vaccine compared to a single dose of Menomune®-A/C/Y/W-135 when given to adults 56 years of age and older.

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

In the US, the incidence rate of IMD was 0.14 per 100,000 in all ages; 0.83 per 100,000 in infants less than 1 year; 0.62 per 100,000 in toddlers 1 year of age; 0.27 per 100,000 in children 2 to 4 years of age; and 0.02 per 100,000 in children 5 to 17 years of age in 2013. The age-specific incidence rate per 100,000 was 0.08 in adults 50 to 64 years of age, 0.03 in adults 65 to 74 years of age, 0.14 in adults 75 to 84 years of age, and 0.43 in adults 85 years of age and older in 2013 (28).

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

1.2 Background of the Investigational Product

1.2.1 Non-clinical Safety

[redacted]

1.2.2 Clinical

The MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 to 55 years of age; and MET32, a Phase I/II study in toddlers.

The formulation has been evaluated in over 650 subjects (infants, toddlers, and adults > 55 years of age) in MET39 and MET44. Both Phase II studies are discussed below. In addition, the vaccine has been evaluated in another Phase II study in 10 to 17 year olds in the US (MET50). The MET50 study evaluated the safety and immune response of the MenACYW conjugate vaccine when administered alone or along with Tdap and HPV vaccine administered concurrently as compared to a licensed vaccine (MENVEO®). A total of 895 subjects received the MenACYW conjugate vaccine in this study. The follow up of this study has been completed; however, analysis is still ongoing. No safety concerns or signals were identified in this study.

The 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.

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, one as a result of hypoxic ischemic encephalopathy which started 96 days after the 6-month vaccination and one 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.

Study MET44 (Phase II)

MET44 was a Phase II, randomized, open-label (the laboratory technicians were blinded to group assignment), multi-center study conducted in the US. This study evaluated the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine when administered to adults 56 years of age and older. A total of 301 subjects age 56 years and older on the day of enrollment were randomized to receive a single dose of MenACYW conjugate vaccine or Menomune® - A/C/Y/W-135; each group was stratified according to age into 2 subsets (subjects 56 to 64 years of age and subjects ≥ 65 years of age). The subjects were randomly allocated to Group 1 or Group 2 with a 2:1 ratio (201 in Group 1 and 100 in Group 2), and stratified according to age into 2 subsets (101 in Group 1a, 100 in Group 1b, 50 in Group 2a, and 50 in Group 2b).

Immunogenicity

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

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

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

Safety

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

Overall, the safety profile in the subset of subjects 56 to 64 years of age was generally comparable to the safety profile in the subset ≥ 65 years of age, with the exception of a small increase in injection site reactions found in the subset 56 to 64 years of age in both study groups.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

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

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

Subjects who receive Menomune® - A/C/Y/W-135 will likely be protected against meningococcal disease caused by *N. meningitidis* serogroups A, C, Y, and W.

As with any vaccine, MenACYW conjugate vaccine and Menomune® - A/C/Y/W-135 may not protect 100% of individuals against the diseases they are designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine or Menomune® - A/C/Y/W-135 may cause injection site reactions such as pain, swelling, and erythema, or certain systemic events such as fever, headache, malaise, or myalgia. There may be a rare possibility of an allergic reaction, which could be severe. There may be other risks for MenACYW conjugate vaccine that are not yet known.

The following additional adverse events have been reported during post-approval use of Menomune® - A/C/Y/W-135: Guillain-Barré syndrome (GBS), vasovagal syncope, dizziness, paresthesia, nausea, vomiting, diarrhea, arthralgia, asthenia, chills, fatigue, and hypersensitivity reactions such as rash, urticaria, pruritus, dyspnea and angioedema. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to Menomune® - A/C/Y/W-135 exposure.

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. This 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 (30). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (31).

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

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

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

The potential risks listed here are not exhaustive. Refer to the package insert of Menomune® - A/C/Y/W-135 (32) and the Investigator's Brochure of the investigational vaccine for additional information regarding the potential risks.

1.4 Rationale for the Trial

The MenACYW conjugate vaccine is designed for the immunization of individuals of all ages (infants 6 weeks of age and older through and including older adults > 65 years of age) against IMD. The purpose of the vaccine is to provide broad coverage against circulating meningococcal strains from serogroups A, C, Y, and W. Compared to a previous Sanofi Pasteur meningococcal 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 MET49 is to demonstrate non-inferiority of immunogenicity and evaluate the safety of a single dose of MenACYW conjugate vaccine compared to a single dose of Menomune® – A/C/Y/W-135 in adults 56 years of age and older in the US.

2 Trial Objectives

2.1 Primary Objectives

To demonstrate the non-inferiority of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine compared to those observed following the administration of a single dose of Menomune® – A/C/Y/W-135.

The endpoints for the primary objectives are presented in Section 9.1.1.1

2.2 Secondary Objectives

1) To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine to those observed following the administration of Menomune® – A/C/Y/W-135

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

2.3 Observational Objectives

Immunogenicity

- To describe antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135
- To describe antibody titers against meningococcal serogroups A, C, Y, and W measured by rSBA at baseline (before vaccination) and 30 days after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 in a subset of 100 subjects per treatment group

Safety

- To describe the safety profile of MenACYW conjugated vaccine compared to that of the licensed Menomune® – A/C/Y/W-135 after a single administration.

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

3 Investigators and Trial Organization

This trial will be conducted in approximately 35 centers in the US. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by one Coordinating Investigator. Details of the trial 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 blinded safety analysis on safety data after vaccination.

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

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form(s) (ICF), subject

recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

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

The Investigator and Sponsor will submit written summaries of the status of the trial to the IEC / IRB annually, or more frequently if requested. All SAEs occurring during the trial that are related to vaccination 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 Trial Design and Plan

5.1.1 Trial Design

This is a Phase III modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® - A/C/Y/W-135 in adults ≥ 56 years of age in the US.

Approximately 900 healthy adults will be randomized in a 1:1 ratio to the following groups:

- Group 1: MenACYW conjugate vaccine
- Group 2: Menomune® - A/C/Y/W-135

Enrollment will be stratified by age (see Table 5.1).

For subjects 56 to 64 years of age, 200 subjects will be enrolled in both Group 1 and Group 2.

For subjects 65 years of age and older, 250 subjects will be enrolled in both Group 1 and Group 2. These subjects will be further stratified into 2 groups as 65 to 74 years of age and 75 years of age and older. At least 25% of the 250 subjects will be enrolled in each of these age groups.

Table 5.1: Testing strategy for *N. meningitidis* serogroups ACYW

	ACYW serogroups tested by hSBA (all subjects)	ACYW serogroups tested by rSBA (subset)
Group 1		
56-64 years	200	50
≥ 65 years:	250	50
65-74 years	70-180	15-35
≥ 75 years	70-180	15-35
Group 2		
56-64 years	200	50
≥ 65 years:	250	50
65-74 years	70-180	15-35
≥ 75 years	70-180	15-35

All subjects will provide pre-vaccination blood samples for immunogenicity assessment at baseline (Visit 1) and at Day (D)30 (+14-day window) post-vaccination (Visit 2). Solicited AE information will be collected for 7 days after vaccination, unsolicited AE information will be collected from Visit 1 to D30 (Visit 2), and SAE information will be collected from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAAEs) will be collected from Visit 1 through Visit 2 (as part of the collection of unsolicited AE information) and from Visit 2 through D180 (+14 days) (as MAAEs).

5.1.2 Justification of the Trial Design

[redacted] MET49 is a study that will be conducted as part of the Phase III of development of the MenACYW conjugate vaccine in which the vaccine would be evaluated in the age group 56 years of age and older.

This study is designed to evaluate immunogenicity responses and safety profiles following the administration of a single dose of the MenACYW conjugate vaccine compared to the responses observed after a single dose of a licensed quadrivalent meningococcal vaccine (Menomune®) in this population.

Conjugation of polysaccharide antigens to a protein carrier can induce T-cell-dependent immune responses, which give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory. Conjugate technology has been successfully applied to Hib, pneumococcal, and meningococcal antigens and has demonstrated improvements in cellular immune responses, and long-term memory. It is well documented that increasing age is associated with a decline in humoral and cell-mediated immunity to both newly-encountered pathogenic

organisms and vaccines. As a consequence, adults ≥ 56 years of age are more susceptible to infection and less responsive to vaccines. This is felt to be attributable to fewer circulating naïve T cells, which also have reduced immune responsiveness relative to T cells in younger individuals.

In addition, there is evidence that T cell immune systems of adults ≥56 years of age are comprised primarily of memory T cells, which are more readily activated than naïve T cells.

It is possible that the ability of MenACYW conjugate vaccine conjugate to confer T cell dependent responses will be observed in adults ≥ 56 years of age and could provide an important mechanism to compensate for the reduction in naïve T cells while further boosting responses in existing memory T cells. Due to more frequent occurrences of chronic illnesses in adults ≥ 56 years of age, the need for repeat vaccination is not uncommon. Another driver of repeat vaccination in this age group is international travel. A conjugate vaccine that could prime, boost, prolong the duration of protection, and not induce hyporesponsiveness would be an important improvement over existing polysaccharide vaccines. Based on these potential responses to a conjugate vaccine in this population, it is expected that MenACYW conjugate vaccine could provide an immunogenicity advantage over those seen after the administration of Menomune® - A/C/Y/W-135 in the population ≥ 56 years of age.

The selection of Menomune® – A/C/Y/W-135 as a comparator will contribute towards the total database of subjects that is compared to the competitor's product in the final dossier and will be beneficial for the Food and Drug Administration (FDA) review of the file, as Menomune® – A/C/Y/W-135 is one of the quadrivalent meningococcal conjugate vaccines licensed in the US.

5.1.3 Trial Plan

Vaccination

All subjects will receive a single dose of either MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 at Visit 1 (D0).

Blood sampling

All subjects will provide a pre-vaccination blood sample at Visit 1 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).
- The subject will record information in a DC 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.
- The subject will record information about any possible SAEs and MAAEs in a memory aid (MA) from Visit 2 until the 6 month (+14 days) telephone call.
- In addition, the subject will be asked to notify the site immediately about any potential SAEs at any time during the trial.

- Staff will contact the subject by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the DC up to Visit 2 and to bring it back to Visit 2.
- The completed DC will be reviewed with the subject at Visit 2.
- Staff will contact the subject by telephone at 6 months (+14 days) after vaccination to review the MA and identify the occurrence of any MAAEs, as well as SAEs that have not been reported.

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 information about the trial, answer any questions, obtain written informed consent, and give him / her a signed copy.
2) Check inclusion and exclusion criteria for eligibility (see Section 5.2.4 and Section 5.2.5, respectively).
3) Collect demographic data.
4) Urine pregnancy test, if applicable
5) Obtain verbal medical history about the subject.
6) 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).
7) Connect to the Interactive Web Response System (IWRS) for randomization, dose number assignment, and allocation of subject number (see Section 6.5 for instructions).
8) Obtain the first blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (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. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.
9) Administer the appropriate study vaccine to the subject in the deltoid region. The vaccine must be administered on the side opposite to that of the blood sampling according to the study group:
   - Group 1 = MenACYW conjugate vaccine
   - Group 2 = Menomune® - A/C/Y/W-135
10) Keep the subject under observation for 30 minutes, and record any adverse event (AE) in the source document.
11) Give the subject a DC, a thermometer, and a ruler, and go over the instructions for their use.

12) Remind the subject to expect a telephone call 8 days after Visit 1 and to bring back the DC when he/she returns for Visit 2 at a specified date and time.

13) Remind the subject to notify the site in case of an SAE.

14) Complete the relevant case report form (CRF) pages for this visit.

Telephone Call 1 (8 to 10 days after Visit 1)

Note: If Day 08 falls on a weekend or a holiday, the telephone call may be made on the following business day. If the subject is not available, the study staff should document the attempts to make contact.

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

2) Remind the subject to do the following:

- Complete the D0 to D07 pages of the DC
- Complete the remaining pages of the DC, and bring them to Visit 2.
- Notify the site in case of an SAE.

Visit 2 (30 [+14] days after Visit 1): Collection of Safety Information and Blood Sample

1) Review the pages of the DC with the subject, including any AEs, medications, or therapy that occurred since vaccination.

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

3) Obtain the second blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).

4) Give the subject an MA.

5) Complete the termination record of the CRF.

6) If the subject does not return for Visit 2, and the DC is not received at the site, site personnel will contact the subject by telephone. During the telephone call, the subject will be reminded to return the DC to the study site. Telephone calls will be documented on the Telephone / Interview Record. If the study personnel are unable to contact the subject with 3 attempts, the study personnel will follow instructions given in Section 5.2.10.

Safety Follow-up Telephone Call (180 [+14] days after Visit 1): Collection of SAEs and MAAEs

Review the MA and ask the subject if he/she has experienced any SAE in the time since vaccination that has not been reported to the study personnel and / or MAAE.

- If an SAE has occurred, follow the instructions in Section 10 for reporting it.
- If an MAAE has occurred, follow the instructions in the Operating Guidelines.

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

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

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

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

5.1.5 Planned Trial Calendar

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

Planned trial period - FVFS to LCLS[a]: 15 July 2016 - 05 May 2017

Planned inclusion period - FVFS to FVLS: 15 July 2016 – 04 November 2016

Planned end of trial: 05 May 2017

Planned date of final clinical study report: March 2018

Safety Follow-up Telephone Call (180 [+14] days after Visit 1) of the last subject in either group is considered to be the end of the trial.

5.1.6 Early Safety Data Review

This trial will not include an early review of safety data (i.e., no early safety review[s] of preliminary safety data occurring at pre-determined milestones defined in the protocol with pause in enrollment). However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in the country where the trial is taking place.

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

5.2 Enrollment and Retention of Trial Population

5.2.1 Recruitment Procedures

Before the start of the trial, the Investigator and / or study staff may contact subjects of an appropriate pool of potential subjects and invite them to participate in the study. The site will

[a] FVFS: First visit of first subject; LCLS: Last contact of last subject; FVLS: First visit of last subject

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.

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

5.2.2 Informed Consent Procedures

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

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

A subject who cannot read will not be included in the trial.

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

If new information becomes available that may be relevant to the subject's willingness to continue participation in the trial, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

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

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

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment:

1) Aged ≥ 56 years on the day of inclusion[a]
2) Informed consent form has been signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures

[a] "≥ 56 years" means from the day of the 56th birthday and older

5.2.5 Exclusion Criteria

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

1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination)
2) 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
3) Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after study vaccine. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.
4) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B vaccine)
5) Receipt of immune globulins, blood or blood-derived products in the past 3 months
6) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)
7) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically
8) At high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease)
9) Known systemic hypersensitivity to latex or 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]
10) Personal history of Guillain-Barré syndrome (GBS)
11) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within at least 10 years of the proposed study vaccination
12) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination, in the Investigator's opinion

[a] The components of MenACYW conjugate vaccine are listed in Section 6.1.1.1 and in the Investigator's Brochure. The components of Menomune® – A/C/Y/W-135 are listed in Section 6.1.2.1 and in the package insert. Menomune® – A/C/Y/W-135: The stoppers to the vials of lyophilized vaccine and diluent contain dry natural latex rubber that may cause allergic reactions in latex sensitive persons.

13) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion
14) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
15) Current alcohol abuse or drug addiction
16) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion[a]
17) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided
18) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
19) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

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

5.2.6 Medical History

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

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

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

The reporting of signs and symptoms is strongly discouraged.

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

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

5.2.7 Contraindications for Subsequent Vaccinations

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

5.2.8 Contraindications for Subsequent Blood Samples

Should a subject receive oral or injectable antibiotic therapy within 3 days before 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 on D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.9 Conditions for Withdrawal

Subjects will be informed that they have the right to withdraw from the trial at any time. A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject's permission
- At the request of the subject (dropout)

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

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

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

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

Withdrawn subjects will not be replaced.

5.2.10 Lost to Follow-up Procedures

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

5.2.11 Classification of Subjects Who Discontinue the Trial

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

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

5.2.12 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the trial because of an SAE, other type of AE, non-compliance with the protocol, or loss of eligibility, including definite contraindications.

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

For subjects where the reason for early termination is voluntary withdrawal, the site will attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.2.13 Follow-up and Reporting of Pregnancies

Pregnancy is an exclusion criterion for enrollment in this study, but a subject could potentially become pregnant during her participation. In case of pregnancy and if the single dose of the study vaccine has been administered, the subject will not be discontinued from the trial and will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

All pregnancy cases should be reported if they occurred during the study and during the 6-month follow-up period, or if the start date of the pregnancy cannot be determined. To report the pregnancy case, the Investigator must fill out a Pregnancy Reporting Form in the electronic data capture (EDC) system and send it to the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome—i.e., details about the delivery and the newborn, or about pregnancy termination—and must update the electronic Pregnancy Reporting Form. This information should be provided to the Sponsor within 1 month of delivery.

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

5.3 Safety Emergency Call

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

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

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

5.4 Modification of the Trial and Protocol

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

An administrative amendment to a protocol is one that modifies some administrative or logistical aspect of the trial but does not affect its design or objectives or have an impact on the subjects' safety. Administrative changes do not require IRB approval; however, the IRB must be notified whenever one is made.

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

5.5 Interruption of the Trial

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

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

6 Vaccines Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Trial Product

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

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

6.1.1.1 Composition

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

Meningococcal capsular polysaccharides:

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

Tetanus toxoid protein carrier .....approximately 65 µg

6.1.1.2 Preparation and Administration

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

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

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

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

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

6.1.1.3 Dose Selection and Timing

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

6.1.2 Identity of Control Product

Menomune® - A/C/Y/W-135: Meningococcal Polysaccharide Vaccine, Groups A, C, Y, W-135 Combined (Sanofi Pasteur Inc., Swiftwater, PA, USA)

Form:	Lyophilized single-dose vial with 0.6-mL vile of diluent (sterile, pyrogen-free distilled water without preservatives
Dose:	0.5 mL
Route:	Subcutaneous
Batch number:	To be determined (Provided by Sponsor)

6.1.2.1 Composition

After reconstitution with diluent as indicated in the Prescribing Information, each 0.5 mL dose contains 50 µg of polysaccharide from each of serogroups A, C, Y, and W-135 (32).

Each dose of vaccine contains 2.5 milligrams (mg) to 5 mg of lactose added as a stabilizer.

6.1.2.2 Preparation and Administration

Refer to Section 6.1.1.2 for general precautions regarding inspection of study products before use.

Menomune® – A/C/Y/W-135 is supplied as a single-dose vial of lyophilized vaccine, with a corresponding single-dose vial of diluent. After reconstitution of the lyophilized vaccine with the diluent, each dose consists of a 0.5 mL suspension for injection.

The vaccine will be reconstituted using only the diluent supplied for this purpose. The supplied diluent (0.6 mL) is to be withdrawn using a suitable syringe and injected into the vial containing the lyophilized vaccine. The vial is to be swirled until the vaccine is thoroughly dissolved. When reconstituted, the vaccine should be a clear, colorless liquid and should be used immediately after reconstitution.

The site of subcutaneous injection should be prepared with a suitable antiseptic prior to administration of 1 dose of Menomune® – A/C/Y/W-135 in the deltoid region of the arm. Using a suitable sterile needle and syringe and aseptic technique, a 0.5 mL dose of Menomune® –

A/C/Y/W-135 should be administered by SC injection. After vaccine administration, the used syringe and needle will be disposed of in accordance with currently established guidelines.

Care will be taken by the Investigator and other trial personnel to ensure the safe and effective use of this vaccine. Prior to injection, all known precautions will be taken to prevent adverse reactions. This includes a review of the subject's history with respect to previous immunizations and to a possible sensitivity to the vaccine or similar vaccine.

Vaccinations should not be given to individuals known to be allergic to any vaccine component. The stopper of the vial of Menomune® – A/C/Y/W-135 contains dry natural latex rubber, to which certain individuals may be allergic.

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 source documents and transferred to the CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

6.1.2.3 Dose Selection and Timing

All subjects in Group 2 will receive one 0.5 mL dose of Menomune® – A/C/Y/W-135 on D0 (Visit 1).

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

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

Commercial lots of Menomune® – A/C/Y/W-135 (supplied in 2 vials that must be combined prior to administration to produce a single dose) will be supplied by the Sponsor.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature recorders). If

there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

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

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

6.3.2.3 Product Accountability

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

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

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

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

6.3.3 Replacement Doses

If a replacement dose is required for MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135 (e.g., because the syringe broke or particulate matter was observed in the syringe), the site personnel must either connect to the IWRS to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

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

6.3.5 Recall of Products

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

6.4 Blinding and Code-breaking Procedures

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

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

The blind can be broken by the Investigator or a sub-investigator (medical doctor only[a]), by connecting to the IWRS as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator must notify the Sanofi Pasteur RMO if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents.

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

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

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

6.5 Randomization and Allocation Procedures

Each subject who signs the ICF and who meets the inclusion / exclusion criteria will be randomly assigned to 1 of 2 trial groups. Site staff will connect to the IWRS, enter the identification and security information, and confirm a minimal amount of data in response to IWRS prompts. The IWRS will then provide the product dose number assignment. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the trial, then the information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IWRS will consist of an 8-digit string (a 3-digit trial center identifier and a 5-digit subject identifier connected by "-"). For example, [redacted].

Subject numbers should not be reassigned for any reason. The Research and Development (R&D) Site Quality Operations Department at Sanofi Pasteur will hold the randomization codes in a secured location.

[a] according to local regulations

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications and Other Therapies

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

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

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

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

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

Note: inhaled and topical steroids should not be captured.

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

- The period of collection should be within 3 days before the first blood draw and up to the last scheduled blood draw.

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

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

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

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

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

7 Management of Samples

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

7.1 Sample Collection

At Visit 1 and Visit 2, 10 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity; will verify the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 Sample Preparation

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

After the blood draw, the sampling 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 subject's consent for future use of his / her samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

7.3 Sample Storage and Shipment

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

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

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

7.4 Future Use of Stored Serum Samples for Research

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

The subjects will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. (Anonymity of samples will be ensured.) The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve laboratory methods. Genetic tests will never be performed on these samples without individual informed consent.

8 Clinical Supplies

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

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

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

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines. They must allow approximately 1 week for an order to be filled and to have the supplies sent to their site.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days after vaccination

9.1.1.2 Immunogenicity Assessment Methods

[redacted]

[redacted]

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the trial.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

The secondary endpoints for immunogenicity are:

1) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine and Menomune® – A/C/Y/W-135

9.2.1.2 Immunogenicity Assessment Methods

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

9.2.2 Safety

There are no secondary objectives for safety.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the trial.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 Immunogenicity Endpoints

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135

9.3.1.2 Immunogenicity Assessment Methods

[redacted]

Antibodies to Meningococcal Antigen (rSBA Method)

[redacted]

9.3.2 Safety

9.3.2.1 Safety Definitions

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

Adverse Event (AE):

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

Therefore an AE may be:

- A new illness
- The worsening of a concomitant illness

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

- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

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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 out-patient treatment with no hospitalization.

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

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

Adverse Reaction:

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

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

Unexpected Adverse Reaction (UAR):

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

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

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

- Symptom and
- Onset post-vaccination

e.g., injection site pain between D0 and D07 after vaccination, or headache between D0 and D07

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

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and / or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D7 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE.

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

Injection Site Reaction:

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

Systemic AE:

Systemic AEs are all AEs that are not injection site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not

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

associated with the vaccination site, e.g., erythema that is localized but that is not at the injection site.

Medically-Attended Adverse Events (MAAEs):

An MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject to seek unplanned medical advice at a physician's office or Emergency Department.

This definition excludes pre-planned medical office visits for routine check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. Physician contact made over the phone or by email will be considered a physician office visit for the purpose of MAAE collection.

The outcome of the physician contact (whether it results in a prescription or not) will not be considered as a basis for reporting the event as an MAAE and all contacts should be reported. Sufficient data should be collected for the event to allow an assessment of the causality and diagnosis, if possible.

9.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's DC and electronic case report form [CRF]) injection site reactions occurring up to 7 days after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's DC and CRF) systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs occurring up to Visit 2.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the trial.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness, relationship to vaccination, and outcome for MAAEs from Visit 2 to the 6-month follow-up contact. MAAEs will be collected as unsolicited AEs up to Visit 2.

9.3.2.3 Safety Assessment Methods

At Visit 2, the Investigator or a delegate will ask the subject about any solicited reactions and unsolicited AEs recorded in the DC, as well as about any other AEs that may have occurred since

the previous visit. All relevant data will be transcribed into the CRF according to the instructions provided by the Sponsor.

9.3.2.3.1 Immediate Post-vaccination Surveillance Period

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

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

9.3.2.3.2 Reactogenicity (Solicited Reactions from Day 0 to Day 7 after Vaccination)

After vaccination, subjects will be provided with a safety DC, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the DC on the day of vaccination and for the next 7 days (i.e., D0 to D07) until resolution:

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

The action taken by the subject to treat any **solicited reactions** will be classified in the CRF using the following scale:

0: None

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

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

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

4: Hospitalization (inpatient)

Subjects will be contacted by telephone 8 days after vaccination to remind them to record all safety information in the DC.

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 DCs and CRF, together with the intensity scales.

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

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
DC term	Pain	Redness	Swelling
Definition		Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

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

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

CRF term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia
DC term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥ 100.4°F (≥ 38.0°C)	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: ≥ 100.4°F to ≤ 101.1°F, **or** ≥ 38.0°C to ≤ 38.4°C Grade 2: ≥ 101.2°F to ≤ 102.0°F **or** ≥ 38.5°C to ≤ 38.9°C Grade 3: ≥ 102.1°F **or** ≥ 39.0°C	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

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

Important notes for the accurate assessment of temperature:

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

9.3.2.3.3 Unsolicited Non-serious Adverse Events from Day 0 to Day 30 after Vaccination

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

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

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

The action taken by the subject to treat any **unsolicited AEs** will be classified in the CRF using the following scale:

0: None

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

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

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

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

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

9.3.2.3.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from Visit 1 until 180 days after vaccination.

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

See Section 10 for further details on SAE reporting.

9.3.2.3.5 Adverse Events of Special Interest

Not applicable.

9.3.2.3.6 Medically-Attended Adverse Events

MAAE information will be collected throughout the study. MAAEs that occur from Visit 1 (D0) to Visit 2 (D30[+14days]) will be recorded as unsolicited AEs on the diary card as part of all unsolicited AEs collected for this post-vaccination period. MAAEs that occur from Visit 2 (D30 [+14 days]) to D180 (+14 days) will be recorded as such in the MA. An MAAE that occurs within the study period but meets the definition of an SAE should be reported only on the SAE Reporting Form, but not on the MAAE page of the CRF. The Investigator will assess the causal relationship between the MAAE and the investigational or study product as either "not related" or "Related," as described in Section 9.3.2.3.7.

9.3.2.3.7 Assessment of Causality

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

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

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

[a] ICH Guidelines, Clinical Safety Data Management E2A

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

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

9.3.3 Efficacy

No clinical efficacy data will be obtained in the trial.

10 Reporting of Serious Adverse Events

In order to comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship, and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product. It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed into the electronic Serious Adverse Events (eSAE) Form.

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the trial or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The SAE form must be signed by a licensed physician (M.D. or D.O.) for whom the task is listed on the Study Task Delegation and Signature List after each update to the Form.

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

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

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

- By fax, to the following number: [redacted]

- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted] (see the Operating Guidelines for directions on how to send a password protected email).
- By express mail, to the following address:

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

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

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

10.2 Follow-up Reporting by the Investigator

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

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

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

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

10.4 Assessment of Causality

The causal relationship between the SAE and the product will first be evaluated by the Investigator, using the following definitions:

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

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

(ICH Guidelines, Clinical Safety Data Management E2A)

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

The decision to modify or discontinue the trial may be made after mutual agreement between the Sponsor and the 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], [redacted], [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 trial protocol.

11 Data Collection and Management

11.1 Data Collection and CRF Completion

Individual safety DCs, specifically designed for this trial by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.3.2.3. The DCs will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Subjects will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects either during a visit or over the telephone using a questionnaire to capture SAEs and AEs of particular interest, if applicable. An MA will be provided to the subjects at the preceding trial visit to help them record information on events occurring between this visit and the 6-month follow-up.

Relevant information will be transcribed into the CRF. Any SAEs captured during this 6-month follow-up period will be reported and followed-up as per the normal process for reporting SAEs.

The clinical team may decide to replace the MA by a diary card if a follow-up visit is planned for the subjects.

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

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

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

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

11.2 Data Management

Management of Clinical Data

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

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

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

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

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

SAE Data Management

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

Upon receipt of an eSAE Form, the data will be entered into the GPV database after a duplicate check. Each SAE case will be assigned a case identification number. Each case will be entered in the GPV database and assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. Assessment of related cases will be done in collaboration with the PSO and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information pertaining to SAEs in the GPV database will be reconciled with that in the clinical database.

11.3 Data Review

A 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 Safety Management Team (SMT). For all periodic safety reviews, blinded safety data will be provided to the Sponsor's SMT.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Clinical data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor. A statistical analysis plan (SAP) will be written and peer reviewed before any analyses. In accordance with the protocol, the SAP will describe all analyses to be performed under the responsibility of the Sponsor and all the conventions to be taken.

12.1.1 Hypotheses and Statistical Methods for Primary Objective

Thirty days after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135, the percentages of subjects who achieve an hSBA vaccine seroresponse[a] for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H_0): $p(G1) - p(G2) \leq -10\%$

[a] hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

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

Alternative hypothesis (H_1): $p(G1) - p(G2) > -10\%$

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

For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions will be computed using the Wilson Score method without continuity correction (33). The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

Descriptive statistics will be presented.

Thirty days after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135, the hSBA geometric mean titer ratio (GMTR) between Group 1 and Group 2 will be calculated and 95% CI will be provided.

12.1.3 Statistical Methods for Observational Objectives

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

Immunogenicity

Descriptive statistics will be provided for the hSBA and rSBA[a] antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and Menomune® – A/C/Y/W-135. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages (34). For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine will be described by:

- GMT and 95% CI
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI

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

Antibody titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days after vaccination with MenACYW conjugate vaccine will be tested and described in a subset of 100 subjects per treatment group by:

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

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 preferred term. For each unsolicited AE, the number of subjects with at least one instance of that event will be reported. Unsolicited AEs will also be tabulated by intensity and relatedness of study vaccine and by other categories specified in the endpoints.

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

12.2 Analysis Sets

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

12.2.1 Full Analysis Set

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

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

12.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received at least 1 dose of the study vaccine and have any safety data available. All subjects will have their safety analyzed according to the vaccine they actually received.

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

12.2.3 Per-Protocol Analysis Set

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample in the proper time window or a post-dose serology sample was not drawn. Time window will be defined as D30 to D44 post-vaccination.
- Subject received a protocol-prohibited Category 2 or Category 3 therapy / medication / vaccine
- Subject's serology sample did not produce a valid test result
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database

12.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS according to randomization group. All safety analyses will be performed on the SafAS. Subjects will be analyzed according to the vaccine they actually received.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

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

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

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

The derived endpoint of fold-rise is computed as follows 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

12.3.3 Efficacy

Not applicable.

12.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

A total of 900 subjects will be enrolled.

[redacted]

[redacted]

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Trial / Good Clinical Practice

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

13.2 Source Data and Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets. The purpose of trial source documents is to document the existence of subjects and to substantiate the integrity of the trial data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

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

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

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

[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.

by the Sponsor or an inspector against the electronic records. Any later changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

13.3 Confidentiality of Data and Access to Subject Records

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

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

In the event a subject's medical records are not at the investigational site, it is the responsibility of the investigator to obtain those records if needed.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

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

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

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

- Evaluate the quality of the trial progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRFs and any corresponding answered
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.

- After all protocol procedures have been completed and the data have been entered into the CRF, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

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

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

13.4.2 Audits and Inspections

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

13.4.3 Archiving

The Investigator must keep all trial documents after the completion or discontinuation of the trial, whatever the nature of the investigational center (private practice, hospital, or institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, trial documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any trial documents upon less than 90 days advance written notification to the Sponsor. In addition, trial documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the trial documents.

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

13.5 Financial Contract and Insurance Coverage

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

13.6 Stipends for Participation

Additionally, address any incentives the subject may receive, other than stipends given to cover their expenses for participating in the study (usually incentives are given for phase I).

13.7 Publication Policy

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

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

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

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15 Signature Pages

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