NCT Number: NCT03869866

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Potential Pilgrims Aged 56 Years and Older

A Phase III, open-label, study to describe the immunogenicity and safety of MenACYW conjugate vaccine in potential pilgrims ≥ 56 years of age in Turkey and Lebanon.

Clinical Study Protocol, Amendment 1

Health Authority File Number:	BB-IND#: NA EudraCT #: NA BGTD File#: NA
WHO Universal Trial Number (UTN):	U1111-1183-6163
Study Code:	MEQ00063
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur 14 Espace Henry Vallée 69007, Lyon France
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:	Potential pilgrims aged 56 years and older
Manufacturer:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Coordinating Investigators	[redacted]
Administrative Supervisor	[redacted]
Sponsor's Responsible Medical Officer:	[redacted]

Project Manager and Study Leader	[redacted]
Global Safety Officer:	[redacted]
Regional Trial Manager:	[redacted]
Version and Date of the Protocol:	Version 5.0 dated 14 Feb 2020

History of Protocol Versions

Previous versions of the protocol

Version*	Date	Comments
1.0	13 October 2017	Internal version not submitted to the Health Authorities and the IEC/IRB
2.0	13 December 2017	Initial version submitted to the Health Authorities and the IEC/IRB
3.0	25 May 2018	Amended version with minor modifications
4.0	17 July 2018	First version used in the study

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Synopsis

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

Title of the Trial:	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Potential Pilgrims Aged 56 Years and Older
Development Phase:	Phase III
Coordinating Investigators:	[redacted]
Trial Center:	This trial will be conducted at several sites in Turkey and Lebanon. The Investigator(s) and site(s) are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	Q2 2019 to Q3 2021
Trial Design and Methodology:	A Phase III, open-label, study to describe the immunogenicity and safety of MenACYW conjugate vaccine in potential pilgrims ≥ 56 years of age in Turkey and Lebanon. A total of 330 healthy adults will be enrolled in the study to receive a single dose of MenACYW conjugate vaccine.

	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). Safety data will be collected as follows: Immediate unsolicited systemic adverse events (AEs) will be collected within 30 minutes after vaccination. Solicited AE information will be collected for 7 days after vaccination; unsolicited non-serious AE information will be collected from Visit 1 to Visit 2, and serious adverse event (SAE) information (including adverse events of special interest [AESIs]) will be collected from Visit 1 through Visit 2. A certificate of vaccination will be given to each subject after vaccination. The individual subject immunogenicity results will be made available to the study investigator once they are available. The investigator will communicate the study results to the individual subjects. Any subsequent clinical intervention, if needed, will be the responsibility of the investigator based on his/ her clinical judgement and outside of the scope of this protocol. If the antibody titers against meningococcal serogroups A, C, W, and Y measured by rSBA did not reach the protective titer of ≥ 1:8 for one of the serogroups included in the vaccine, the Investigator will advise whether, in light of a potential pilgrimage for Hajj or Umrah in the following 5 years, vaccination with a licensed quadrivalent meningococcal conjugate vaccine will be necessary.
Interruption of the Study	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the countries where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.
Objectives:	*Immunogenicity* • To describe the antibody response to meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using baby rabbit complement (rSBA) before and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine • To describe the antibody response to meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) before and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine • To describe the antibody responses against tetanus toxoid at baseline and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine *Safety* To describe the safety profile of a single dose of MenACYW conjugate vaccine

Endpoints:	*Immunogenicity*
	• Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y measured by rSBA assessed at 30 days (+14 days) after vaccination with a single dose of MenACYW conjugate vaccine
	• Antibody titers against meningococcal serogroups A, C, W, and Y measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine
	• Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine
	• Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested for anti-tetanus antibodies by electrochemiluminescence (ECL). The following endpoints will be assessed:
	  • Antibody concentrations to tetanus toxoid at both pre-and post-vaccination time points, geometric mean concentrations (GMCs)
	  • The proportion of subjects achieving seroprotective levels ≥ 0.01 international Units (IU) / milliliter (mL) and ≥ 0.1 IU/mL of antibody concentrations to tetanus toxoid at both pre- and post-vaccination time points

	Safety • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, relationship to vaccination, and whether the event led to early termination for the study of any unsolicited systemic AEs reported in the 30 minutes after vaccination. • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and electronic case report book [CRB]) injection site reactions occurring up to 7 days after vaccination. • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to 7 days after vaccination. • Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited non-serious AEs occurring up to Visit 2. • Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs (including AESIs) throughout the trial.
Planned Sample Size:	A total of 330 subjects are planned to be enrolled with an expected dropout rate of 15% (280 evaluable subjects planned). In order to balance the age of subjects at enrollment, between 50 and 130 enrolled subjects should be ≥ 75 years of age.

Schedule of Study Procedures:	Vaccination All subjects will receive a single dose of MenACYW conjugate vaccine at Visit 1 (D0). Blood sampling All subjects will provide a pre-vaccination blood sample 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 followed for safety from Visit 1 (D0) to Visit 2 after vaccination • All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the CRB. • The subject will record information in a diary card about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to Visit 2. • SAEs (including AESIs) will be recorded throughout the duration of the trial. The subject will record information in a diary card about SAEs from D0 to Visit 2. • The subject will be asked to notify the site immediately about any potential SAEs at any time during the trial.
	• Staff will contact the subjects by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card up to Visit 2 and to bring it back to Visit 2. • The completed diary card will be reviewed with the subject at Visit 2.
Duration of Participation in the Trial:	The duration of each subject's participation in the trial will be 30 to 44 days.
Investigational Product:	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Form:	Liquid solution
Composition:	Each 0.5 mL dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients: Meningococcal capsular polysaccharides: Serogroup A ..... 10 micrograms (µg) Serogroup C ..... 10 µg Serogroup Y ..... 10 µg Serogroup W ..... 10 µg Tetanus toxoid protein carrier ..... approximately 55 µg* * Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation.
Route:	Intramuscular (IM)
Batch Number:	To be determined

Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) Aged ≥ 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 4) Intending to go on a Hajj or Umrah pilgrimage (but not within the next 10 to 12 months after vaccination)
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 and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile). 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) Any previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, B, C, W, or Y) 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) 9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances 10) Personal history of Guillain-Barre 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 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 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 (eg, human immunodeficiency virus [HIV], hepatitis B, hepatitis C) 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 ≥ 38.0°C). 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 (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

Statistical Methods:	All analyses will be descriptive. No hypotheses will be tested.
	Immunogenicity
	Immunogenicity results will be described. The reverse cumulative distribution curves (RCDCs) and distribution tables will also be produced. The parameters will be described with 95% confidence interval (CI).
	The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages.
	For geometric mean titers (GMTs) or geometric mean concentrations (GMCs) 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.
	In summary, descriptive analyses on A, C, W, and Y serogroups will include but not be limited to:
	• rSBA GMT at D0 and D30
	• rSBA GMT ratio (GMTR) (D30/D0)
	• rSBA titer distribution at D0 and D30
	• Percentage of subjects with rSBA titer ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination (D30)
	• rSBA vaccine seroresponse rate based on D0 and D30 rSBA titers, defined as:
	  • Subjects with a pre-vaccination rSBA titer (D0) < 1:8 and a post-vaccination rSBA titer (D30) ≥ 1:32,
	  • Subjects with a pre-vaccination rSBA titer (D0) ≥ 1:8 and ≥ 4-fold increase of the rSBA titer (individual ratio D30/D0)
	• Percentage of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 at D0 and D30

	• hSBA GMT at D0 and D30
	• hSBA GMTR (D30/D0)
	• hSBA titer distribution at D0 and D30
	• Percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 at D0 and D30
	• Percentage of subjects with hSBA titer ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination (D30)
	• hSBA vaccine seroresponse rate based on D0 and D30 hSBA titers, defined as:
	  • Subjects with a pre-vaccination hSBA titer (D0) < 1:8 and a post-vaccination hSBA titer (D30) ≥ 1:16,
	  • Subjects with a pre-vaccination hSBA titer (D0) ≥ 1:8 and ≥ 4-fold increase of the hSBA titer (individual ratio D30/D0).

	Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested for anti-tetanus antibodies by ECL. The following parameters will be assessed: • Geometric mean concentrations (GMCs) at D0 and D30 • Percentage of subjects achieving seroprotective levels ≥ 0.01 IU/mL and ≥ 0.1 IU/mL of antibody concentrations to tetanus toxoid at D0 and D30 ***Safety*** Safety results will be descriptive. The 95% CIs of point estimates will be calculated using the exact binomial distribution (Clopper-Pearson method) for percentages. **Calculation of Sample Size** The sample size was arbitrarily chosen to be 280 evaluable subjects. Assuming an attrition rate of approximately 15%, a total of 330 subjects will be included in the study. In order to balance the age of subjects at enrollment, between 50 and 130 enrolled subjects should be ≥ 75 years of age. Assuming seroprotection rates of 95% or more (rSBA), a sample size of 280 evaluable subjects per group will ensure a 95% CI with a precision of no more than 5.4% (using the exact binomial method). Assuming seroprotection rates of 75% or more (hSBA), a sample size of 280 evaluable subjects per group will ensure a 95% CI with a precision of no more than 10.5% (using the exact binomial method). In terms of safety, the planned sample size will allow for identification of common AEs. A sample size of 280 evaluable subjects allows, with 95% probability, for the detection of an AE occurring with a frequency of 1.1% or more, using the rule of threes.

Table of Study Procedures

Phase III Trial, 2 Visits, 1 Vaccination, 2 Blood samples, 1 Telephone call,
30 to 44 Days duration per Subject

Visit/Contact	**Visit 1**	**Telephone Call**	**Visit 2**
Trial timelines (days)	D0	D08	D30
Time windows (days)	NA	+2 days	+14 days
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Urine pregnancy test (if applicable)	X		
Medical history	X		
Physical examination*	X		
Allocation of subject number	X		
Review of temporary contraindications for blood sampling†			X
Blood sampling (BL), 10 mL‡	BL0001		BL0002
Vaccination	X		
Immediate surveillance (30 min)	X		
Diary card provided	X		
Telephone call		X§	
Recording of solicited injection site and systemic reactions	D0 to D07		
Recording of unsolicited non-serious AEs	Visit 1 through Visit 2		
Diary card reviewed and collected			X
Reporting of SAEs (including AESIs)**	To be reported throughout the study period		
Collection of reportable concomitant medications	X		X
Trial termination record			X

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

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

§ 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 diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2.

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

List of Abbreviations

µg	microgram
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CDM	Clinical Data Management
CFU	colony-forming unit
CI	confidence interval
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CTA	clinical trial agreement
D	day
DC	diary card
DTP	diphtheria, tetanus, pertussis
ECL	electrochemiluminescence
EDC	electronic data capture
EEA	European Economic Area
EU	European Union
FAS	full analysis set
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global Pharmacovigilance
GSO	Global Safety Officer
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IMD	invasive meningococcal disease
IM	intramuscular
IME	important medical event
IND	investigational new drug (application)
IOM	Institute of Medicine
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IU	international units
KSA	Kingdom of Saudi Arabia
LLOQ	lower limit of quantification
LLT	lowest level term
LVLS	last visit last subject
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
PS	polysaccharide
PT	preferred term
PV	Pharmacovigilance
RCDC	reverse cumulative distribution curve
RME	Regional Medical Expert
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
TMF	trial master file
ULOQ	upper limit of quantification
WHO	World Health Organization

1 Introduction

1.1 Background

This trial (MEQ00063) will describe the immunogenicity and safety profiles 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 adult pilgrims 56 years of age and older.

This is a study using MenACYW conjugate vaccine against meningococcal disease.

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 (KSA) (4) (6) (7) and more recently in Chile (8), Turkey (9) (10), China (11) (12), Argentina (13), and Brazil (14) (15) and in other parts of the world. Serogroup X causes substantial meningococcal disease in parts of Africa but rarely causes disease in other parts of the world (2) (16). Serogroup Y has not been associated with outbreaks, but its frequency as a cause of sporadic cases has gradually increased in the United States (US) and more recently in Canada and Europe (17) (18) (19). This serogroup is commonly associated with meningococcal pneumonia, particularly in older adults > 65 years of age (20). Outbreaks of serogroup B meningococcal disease have also been reported on college campuses in the US during the last 5-year period: a prolonged outbreak of serogroup B on a university campus in Ohio from 2008-2010 and 2 universities in New Jersey and California in 2013 (21) (22).

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

The overall incidence rate of IMD in European Union (EU)/European Economic Area (EEA) countries was 0.68 per 100,000 (ranged from 0.11 to 1.77). The incidence per 100,000 in the study countries ranged from 0.72 in Spain to 0.52 in Hungary in 2012. The highest incidence rate of 5.10 per 100,000 was observed in children < 5 years of age in EU/EEA countries (24).

Data on meningococcal disease in the Middle East and North Africa is scarce (25). Reported incidence rates in recent years varies between < 0.1 cases to 13.26 cases /100,000 population (25). Children younger than 5 years of age are the age group most affected by IMD (9) (25) (26).

Every year more than 2 million people from all over the world undertake the Hajj, the annual pilgrimage to Mecca (27). The Hajj is an epidemiological phenomenon. Because of crowds, high humidity, and air pollution, the carriage rate of *N. meningitidis* can be as high as 80% which eventually may cause epidemics (28) (29). Epidemics during the Hajj have been known for decades (29). After the first documented international outbreak caused by serogroup A, vaccination was mandated for pilgrims to enter the KSA. Starting in 2002, following serogroup-W outbreaks in 2000 and 2001, the requirement for vaccination with bivalent AC vaccine was switched to quadrivalent (ACYW) polysaccharide vaccine (29). Visitors arriving for the purpose of Umrah or pilgrimage (Hajj) are required to submit a certificate of vaccination with the tetravalent (ACYW135) vaccine against meningitis, proving the vaccine was administered no less than 10 days before arrival in Saudi Arabia. Both polysaccharide and conjugate vaccines are valid options.

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

1.2 Background of the Investigational Product

1.2.1 Clinical

The MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 to < 40 years of age; and MET32, a Phase I/II study in toddlers (30).

The formulation has been evaluated in over 2046 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in completed studies MET39, MET44, MET50, MET54, and MET56. MenACYW conjugate vaccine is also being evaluated in ongoing Phase III studies (MET51 and MET57 in toddlers (12 to 23 months of age), MET35 in children (2 to 9 years of age), MET43 (15 to 55 years of age) and MET49 in older adults ≥ 56 years of age.

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

The relevant studies are discussed below.

1.2.1.1 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 serum bactericidal assay using human complement (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-135 among adults 56 years of age and older was found to be well tolerated, with no safety concerns identified. There were no immediate unsolicited AEs/reactions reported in either group. There were no deaths, serious adverse events (SAEs) or adverse events (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.

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

1.2.1.2 Study MET49 (Phase III)

MET49 is a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial currently being conducted in the US. The goal of the study is to evaluate the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine when administered to adults 56 years of age and older. Approximately 900 healthy adults were randomized to receive a single dose of either MenACYW conjugate vaccine or Menomune® - A/C/Y/W-135 in a 1:1 ratio.

For subjects 56 to 64 years of age, 200 subjects were to be enrolled in each group.

For subjects 65 years of age and older, 250 subjects were to be enrolled in each group. These subjects were 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 were to be enrolled in each of these age groups.

The study is ongoing. No new safety signals or safety concerns have been identified as a part of the ongoing review of the study.

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.

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

1.3.2 Potential Risks to Subjects

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

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

Guillain-Barré syndrome (GBS) has been reported mostly in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of a US licensed meningococcal conjugate vaccine (31). A retrospective cohort study carried out in the US using healthcare claims data found no evidence of increased GBS risk associated with the use of that vaccine. The study was able to exclude all but relatively small incremental risks (32).

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 (33). The IOM found evidence for a causal relationship between tetanus toxoid-containing vaccines and brachial

neuritis (34). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (35).

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

The risk of vasovagal syncope exists after any vaccination, although it has not been specifically reported in the age group under study as part of this protocol (36).

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

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

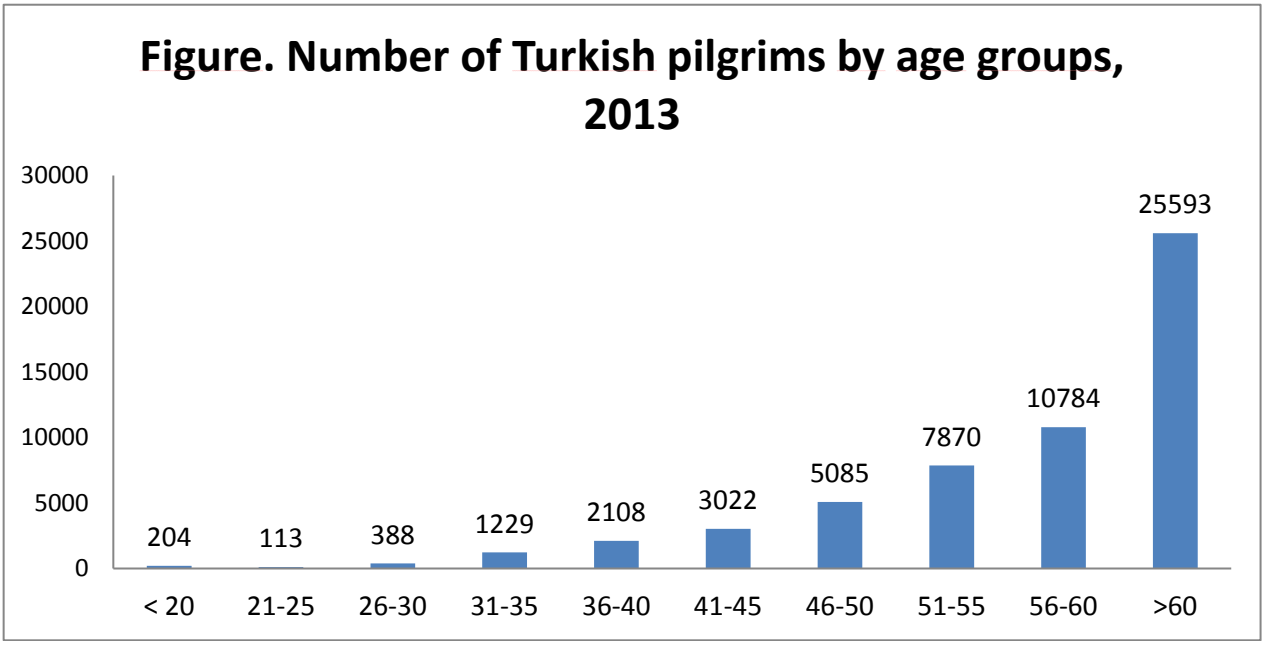
1.4 Rationale for the Study

The KSA has a long history of instituting preventative measures against meningococcal disease. KSA is at risk of outbreaks of meningococcal disease due to its geographic location, demography, and especially because it hosts the annual Hajj and Umrah mass gatherings.

The mandatory meningococcal vaccination policy for pilgrims has possibly been the major factor in preventing outbreaks during the pilgrimages and has also probably been important in reducing the carriage and transmission of *Neisseria meningitidis* in KSA and beyond. The preventative measures for Hajj and Umrah favor the conjugate vaccine for its extra benefits over the polysaccharide vaccines. The Hajj in 2012 and 2013 attracted more than 5 million pilgrims from 184 countries. Most of these pilgrims are part of the elderly population.

Figure 1.1 presents Turkish pilgrims by age (37).

Figure 1.1: Turkish pilgrims by age



2 Study Objectives

Immunogenicity

- To describe the antibody response to meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using baby rabbit complement (rSBA) before and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine
- To describe the antibody response to meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) before and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine
- To describe the antibody responses against tetanus toxoid at baseline and 30 days (+14 days) after a single dose of MenACYW conjugate vaccine

Safety

To describe the safety profile of a single dose of MenACYW conjugate vaccine

The endpoints for the immunogenicity objectives are presented in Section 9.1, and the endpoints for the safety objectives are presented in Section 9.2.

3 Investigators and Study Organization

This study will be conducted in several centers in Turkey and Lebanon. Details of the study centers and the Principal Investigators are provided in the "List of Investigators and Centers Involved in the Trial" document.

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

4 Independent Ethics Committee / Institutional Review Board

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

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

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

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This is a Phase III, open-label, study to describe the immunogenicity and safety of MenACYW conjugate vaccine in potential pilgrims ≥ 56 years of age in Turkey and Lebanon.

Approximately 330 healthy adults will be enrolled in the study to receive a single dose of MenACYW conjugate vaccine.

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).

Safety data will be collected as follow: Immediate unsolicited systemic adverse events (AEs) will be collected within 30 minutes after vaccination. Solicited AE information will be collected for 7 days after vaccination, unsolicited AE information will be collected from Visit 1 to Visit 2, and SAE information (including adverse events of special interest [AESIs]) will be collected from Visit 1 through Visit 2.

A certificate of vaccination will be given to each subject after vaccination. The individual subject immunogenicity results will be made available to the study investigator once they are available. The investigator will communicate the study results to the individual subjects. Any subsequent clinical intervention, if needed, will be the responsibility of the investigator based on his/ her clinical judgement and outside of the scope of this protocol. If the antibody titers against meningococcal serogroups A, C, W, and Y measured by rSBA did not reach the protective titer of ≥ 1:8 for one of the serogroups included in the vaccine, the Investigator will advise whether, in light of a potential pilgrimage for Hajj or Umrah in the following 5 years, vaccination with a licensed quadrivalent meningococcal conjugate vaccine will be necessary.

5.1.2 Justification of the Study Design

MenACYW conjugate vaccine is expected to obtain the age indication over 55 years of age on the basis of the data generated in a well-designed and powered non-inferiority study versus Menomune conducted in the US (MET49). However, no data is available in the specific population of pilgrims representing several millions of people worldwide every year (see Section 1.4).

The proposed study will generate descriptive data on MenACYW conjugate vaccine in a population of potential pilgrims and will be designed according to the same criteria used for the pivotal study MET49.

5.1.3 Study Plan

Vaccination

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

Blood sampling

All subjects will provide a pre-vaccination blood sample 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 followed for safety from Visit 1 (D0) to Visit 2.
- 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 case report book (CRB).
- The subject will record information in a diary card about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to Visit 2.

- SAEs (including AESIs) will be recorded throughout the duration of the trial. The subject will record information in a diary card about SAEs from D0 to Visit 2.
- The subject will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- Staff will contact the subjects by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card up to Visit 2 and to bring it back to Visit 2.
- The completed diary card will be reviewed with the subject at Visit 2.

5.1.4 Visit Procedures

Visit 1 (Day 0): Inclusion, Randomization, and Vaccination

1) Give the subject information about the study, obtain written informed consent, and give him / her a signed copy.
2) Check inclusion and exclusion criteria for eligibility.
3) Collect demographic data.
4) Perform urine pregnancy test (if applicable)
5) Obtain verbal medical history about the subject, including ongoing medication.
6) Conduct a physical examination. Temperature needs to be measured and recorded in source documents.
7) Assign a subject number.
8) Obtain the first blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
9) Administer the study vaccine intramuscularly to the subject in the deltoid region. The vaccine must be administered on the side opposite to that of the blood sampling.
10) Keep the subject under observation for 30 minutes and record any adverse reaction in the source document.
11) Give the subject a subject participation card, a diary card, 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 diary card when he or 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 forms (CRFs) for this visit.

Telephone Call (8 days after Visit 1)

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

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 pages D0 to D07 of the diary card.
    - Complete the remaining pages of the diary card 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) Obtain information on D0 to D07 from the diary card. Review the pages of the diary card with the subject, including any AEs, medications, or therapy that occurred since vaccination.
2) Review the temporary contraindications for Visit 2 blood draw (see Section 5.2.8).
3) Obtain the second blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
4) Complete the relevant CRFs for this visit.

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

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

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

5.1.5 Planned Study Calendar

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

Planned study period - FVFS (first visit, first subject) to LVLS (last visit last subject): April 2019 to July 2021

Planned inclusion period - FVFS to FVLS (first visit, last subject): April 2019 to June 2021

Planned end of study: July 2021

Planned date of final clinical study report: May 2022

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

The site will be responsible for devising a recruitment plan for enrolling eligible subjects. Any document aiming at patients will be approved by Sanofi Pasteur and the coordinating investigator's site's IRB/IEC prior to use by the clinical site.

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 study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

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

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

The actual ICF used at the center may differ from the sample ICF provided by the Sponsor, depending on local regulations and IEC / IRB requirements. However, it 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 study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

Informed consent forms 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 to be eligible for study 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
4) Intending to go on a Hajj or Umrah pilgrimage (but not within the next 10 to 12 months after vaccination)

[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 study enrollment:

1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile).
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 (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, B, C, W, or Y).
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).
9) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances[a].
10) Personal history of Guillain-Barre 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 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.

[a] The components of MenACYW conjugate vaccine are listed in Section 6.1 and in the Investigator's Brochure.

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 (eg, human immunodeficiency virus [HIV], hepatitis B, hepatitis C) 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 ≥ 38.0°C). 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 (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study.

5.2.6 Medical History

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

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

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

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

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

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable.

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

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

- At the discretion of the Investigator or Sponsor due to safety concerns or significant non-compliance with the protocol (based on the Investigator's judgment), without the subject's permission (withdrawal)
- At the request of the subject (dropout)

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

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

Withdrawn subjects will not be replaced.

5.2.10 Lost to Follow-up Procedures

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

5.2.11 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.2.1. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.10. The certified letter was sent by the Investigator and returned unsigned, and the subject did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant non-compliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is a protocol deviation. • The subject signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit.
Withdrawal by Subject	To be used: • When the subject indicated unwillingness to continue in the study • When the subject made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, informed consent withdrawal, etc.)

5.2.12 Follow-up of Discontinuations

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

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

5.2.13 Follow-up and Reporting of Pregnancies

All pregnancy cases should be reported if they occurred during the study. To report the pregnancy case, the Investigator must fill out Pregnancy Reporting forms in the electronic data capture (EDC) system and inform the Sponsor within 1 month of identifying a pregnancy case.

If the EDC system is not available, the Investigator must fill out a paper Pregnancy Reporting Form (provided by the Sponsor at the start of the study) and inform the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome (ie, details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be

provided to the Sponsor within 1 month of delivery. Study staff will ask for information to be provided about the mother and her baby for at least 1 year after the birth.

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

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on a study related medical question or problem.

If the RMO is not available, then the Investigator may contact the Local Medical Information Manager (as described in the study Operating Guidelines).

The contact details will be described in the Operating Guideline.

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

5.4 Modification of the Study and Protocol

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

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. All protocol amendments should be approved in advance by the Ministry of Health to be effective.

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

5.5 Interruption of the Study

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s)

used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.

6 Vaccines Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product

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

Form: Liquid solution

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.1.1.1 Composition

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

Meningococcal capsular polysaccharides:

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

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

6.1.1.2 Preparation and Administration

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

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

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

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

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

6.1.1.3 Dose Selection and Timing

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

6.1.2 Identity of Control Products

Not applicable.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

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

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

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

6.3.2.2 Product Storage

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

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

6.3.2.3 Product Accountability

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

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

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

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

6.3.3 Replacement Doses

If a replacement dose is required (eg, because the syringe broke or particulate matter was observed in the syringe), the site personnel must follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

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

6.3.5 Recall of Products

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

6.4 Blinding and Code-breaking Procedures

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

6.5 Randomization and Allocation Procedures

Subjects will not be randomized.

On the day of enrollment, a subject who signs the ICF and who meets the inclusion / exclusion criteria will be assigned a subject number.

Subject numbers will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example, Subject 792000100005 is the fifth subject enrolled in Center Number 1 in Turkey (792 being the Turkey country code) and Subject 422000100004 is the fourth subject enrolled in Center Number 1 in Lebanon (422 being the Lebanon country code).

Subject numbers should not be reassigned for any reason.

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications and Other Therapies

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

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) 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 CRB from the day of vaccination to the end of the solicited and unsolicited follow-up periods.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], steroids/corticosteroids).
- Category 2: medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Global Clinical Immunology [GCI] department, steroids/corticosteroids, immune-suppressors,

immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors).

- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, steroids/corticosteroids)

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

- Trade name
- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables.
- Medication category (1, 2, or 3)
- Start and stop dates

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

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

7.1 Sample Collection

At Visits 1 and 2, 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 write the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 Sample Preparation

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

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

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

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

7.3 Sample Storage and Shipment

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

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

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

7.4 Future Use of Stored Serum Samples for Research

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

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

8 Clinical Supplies

Sanofi Pasteur will supply the study site with protocols, ICFs, CRBs, SAE reporting forms, diary cards, and other study documents, as well as with the following study materials: all study

vaccines, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

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

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

In the event that additional supplies are required, study staff must contact Sanofi Pasteur Clinical Logistics Coordinator and / or Service Provider, indicating the quantity required. Contact information is provided in the Operating Guidelines.

9 Endpoints and Assessment Methods

9.1 Immunogenicity

The endpoints for the evaluation of immunogenicity are:

- Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y measured by rSBA assessed at 30 days (+14 days) after vaccination with a single dose of MenACYW conjugate vaccine
- Antibody titers against meningococcal serogroups A, C, W, and Y measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine
- Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine
- Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested for anti-tetanus antibodies by electrochemiluminescence (ECL). The following endpoints will be assessed:
  - Antibody concentrations to tetanus toxoid at both pre- and post-vaccination time points, geometric mean concentrations (GMCs)
  - The proportion of subjects achieving seroprotective levels ≥ 0.01 International Units (IU) / milliliters (mL) and ≥ 0.1 IU/mL of antibody concentrations to tetanus toxoid at both pre- and post-vaccination time points

9.1.1 Immunogenicity Assessment Methods

The following methods will be performed on all blood samples (BL0001 and BL0002). In the event of insufficient serum sample volume, the priority of titrations is rSBA, hSBA, and anti-tetanus.

Antibodies to meningococcal antibodies (rSBA method)

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

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

Antibodies to meningococcal antigens (hSBA Method)

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

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

Anti-Tetanus Antibodies

Anti-tetanus antibodies will be measured by ECL.

The Diphtheria, Tetanus, and Pertussis ECL is a multiplexed serological assay which allows for the simultaneous quantification of human antibodies to 6 specific antigens including diphtheria toxoid, tetanus toxoid, and 4 pertussis antigens: pertussis toxin, filamentous haemagglutinin, fimbriae and pertactin.

In this assay, each well of a 96-well microtiter plate is pre-coated in precise positions with the 6 different antigens in a multi-spot fashion. Following incubation with serum samples, antigen-specific antibodies bind to the respective antigens. The captured antibodies are then detected using a sulfotag conjugated anti-human IgG conjugate. Electrical stimulation of the conjugate in the presence of a chemiluminescent substrate results in the generation of a light signal from each specific spot that is captured by a camera in relative light units. The signal generated is directly proportional to the amount of antibodies present in the sample, which is quantified using software

and based on an established reference standard sample curve. For this study, only tetanus results will be calculated.

The anti-tetanus ECL will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

9.2 Safety

9.2.1 Safety Definitions

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

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

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

Adverse Reaction:

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)

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

Solicited Reaction:

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

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

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

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

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

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

The assessment of these reactions by the Investigator is mandatory.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D07 is a solicited reaction (ie, prelisted in the protocol and CRB), then a headache starting on D07 is a solicited reaction, whereas headache starting on D08 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

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

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

9.2.2 Safety Endpoints

The endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, relationship to vaccination, and whether the event led to early termination from the study of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and electronic case report book [CRB]) injection site reactions occurring up to 7 days after vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs occurring up to Visit 2.

- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs (including AESIs) throughout the trial.

9.2.3 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 diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.2.3.1 Immediate Post-vaccination Observation Period

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

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

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

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

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

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

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

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

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

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

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

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

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

Important notes for the accurate assessment of temperature:

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

9.2.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, 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 diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from the time of vaccination until 30 days (+14 days) after vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports).

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

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

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

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

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

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

- Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

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

- Action taken for each AE (eg, medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- Whether the AE was serious

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

- Whether the AE caused study discontinuation

9.2.3.4 Adverse Events of Special Interest

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

Generalized seizures (febrile and non-febrile) (38)

Kawasaki disease (39) (40) (41)

Guillain-Barré syndrome (42)

Idiopathic thrombocytopenic purpura (ITP) (43) (44)

These events have been listed as AESIs on the basis of the feedback received from the EU regulators for other studies (conducted in younger age groups).

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

9.2.3.5 Assessment of Causality

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

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

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

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

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

9.3 Efficacy

There are no objectives for efficacy in this study.

10 Reporting of Serious Adverse Events

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

10.1 Initial Reporting by the Investigator

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

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

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

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

- By fax, to the following number: [redacted]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted]
- By express mail, to the following address:
- Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global PharmacoVigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370

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

If there is need for urgent consultation, the Investigator is to contact the RMO, [redacted]. If the RMO cannot be reached, the Investigator may contact the Local Medical Information Manager as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

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

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

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

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

10.4 Assessment of Causality

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

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

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

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

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

The Sponsor will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the study protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study site, will be given to study participants for the recording of daily safety information as described in Section 9.2.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. 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 site will instruct subjects on how to correctly use these tools.

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.

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

All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of

the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

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

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

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

11.2 Data Management

Management of SAE and Pregnancy Data

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

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

Management of Clinical and Laboratory Data

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

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

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

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

11.3 Data Review

A review of the data is anticipated through the data review process led by Data Management before database lock. The safety of the investigational product will be continuously monitored by the Sponsor.

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 the Objectives

12.1.1.1 Hypotheses

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

12.1.1.2 Statistical Methods

Immunogenicity

Immunogenicity results will be described. The reverse cumulative distribution curves (RCDCs) and distribution tables will also be produced. The parameters will be described with 95% confidence interval (CI).

The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages.

For geometric mean titers (GMTs) or geometric mean concentrations (GMCs) 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

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

- rSBA GMT at D0 and D30

- rSBA GMT ratio (GMTR) (D30/D0)
- rSBA titer distribution at D0 and D30
- Percentage of subjects with rSBA titer ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination (D30)
- rSBA vaccine seroresponse[a] rate based on D0 and D30 rSBA titers
- Percentage of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 at D0 and D30
- hSBA GMT at D0 and D30
- hSBA GMTR (D30/D0)
- hSBA titer distribution at D0 and D30
- Percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 at D0 and D30
- Percentage of subjects with hSBA titer ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination (D30)
- hSBA vaccine seroresponse[b] rate based on D0 and D30 hSBA titers

Tetanus toxoid is contained in the investigational vaccine as a carrier protein. Therefore, blood samples will also be tested for anti-tetanus antibodies by ECL. The following parameters will be assessed:

- Geometric mean concentrations (GMCs) at D0 and D30
- Percentage of subjects achieving seroprotective levels ≥ 0.01 IU/mL and ≥ 0.1 IU/mL of antibody concentrations to tetanus toxoid at D0 and D30

Safety

Safety results will be descriptive. The 95% CIs of point estimates will be calculated using the exact binomial distribution (Clopper-Pearson method) for percentages.

[a] rSBA vaccine seroresponse rate based on D0 and D30 rSBA titers, defined as:

- Subjects with a pre-vaccination rSBA titer (D0) < 1:8 and a post-vaccination rSBA titer (D30) ≥ 1:32,
- Subjects with a pre-vaccination rSBA titer (D0) ≥ 1:8 and ≥ 4-fold increase of the rSBA titer (individual ratio D30/D0)

[b] hSBA vaccine seroresponse rate based on D0 and D30 hSBA titers, defined as:

- Subjects with a pre-vaccination hSBA titer (D0) < 1:8 and a post-vaccination hSBA titer (D30) ≥ 1:16,
- Subjects with a pre-vaccination hSBA titer (D0) ≥ 1:8 and ≥ 4-fold increase of the hSBA titer (individual ratio D30/D0).

12.2 Analysis Sets

12.2.1 Full Analysis Set

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

12.2.2 Safety Analysis Set

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

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

12.2.3 Per-Protocol Analysis Set

The **per-protocol analysis set (**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
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample at Visit 2 in the proper time window (Visit 1 + 30 to 44 days) or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy / medication / vaccine as defined below:
    - Any vaccine in the 4 weeks (28 days) preceding the trial vaccination or prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after study vaccine.
    - 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), or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks in the 3 months preceding the trial vaccination and the 4 weeks following the trial vaccination)
    - Oral or injectable antibiotics within 3 days prior to study blood draw

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

- Subject's serology sample at Visit 2 did not produce a valid test result (ie, results for all antigens are missing).
- Subject had another protocol deviation 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. All safety analyses will be performed on the SafAS.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

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

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

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

The derived endpoint of fold-rise is computed as follows:

- Calculate the fold-rise of values as the ratio of post-baseline computed value divided by baseline computed value
- If baseline or post baseline value is missing, then the seroconversion is missing.

12.3.3 Efficacy

There is no efficacy objective.

12.4 Interim / Preliminary Analysis

No preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

The sample size was arbitrarily chosen to be 280 evaluable subjects. Assuming an attrition rate of approximately 15%, a total of 330 subjects will be included in the study. In order to balance the age of subjects at enrollment, between 50 and 130 enrolled subjects should be ≥ 75 years of age.

Assuming seroprotection rates of 95% or more (rSBA), a sample size of 280 evaluable subjects per group will ensure a 95% CI with a precision of no more than 5.4% (using the exact binomial method).

Assuming seroprotection rates of 75% or more (hSBA), a sample size of 280 evaluable subjects per group will ensure a 95% CI with a precision of no more than 10.5% (using the exact binomial method).

In terms of safety, the planned sample size will allow for identification of common AEs. A sample size of 280 evaluable subjects allows, with 95% probability, for the detection of an AE occurring with a frequency of 1.1% or more, using the rule of threes.

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Study / Good Clinical Practice

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

13.2 Source Data and Source Documents

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

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

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

If electronic medical records are used, the Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as

[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.

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

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

13.3 Confidentiality of Data and Access to Subject Records

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

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

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

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

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

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

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

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries

- Determine the number of complete or ongoing issues identified at monitoring visits (eg, protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

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

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

13.4.2 Audits and Inspections

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

13.4.3 Archiving

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

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

13.5 Financial Contract and Insurance Coverage

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

13.6 Stipends for Participation

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

13.7 Publication Policy

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

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

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

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15 Signature Page

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