NCT04368429

AMENDED CLINICAL STUDY PROTOCOL 01

Immunogenicity and Safety of a Single Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Children, Adolescents, and Adults 2 to 55 Years of Age

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate the immune non-inferiority of MenACYW conjugate vaccine versus Menactra®, and describe the safety and additional immunogenicity of study vaccines in children, adolescents and adults 2 to 55 years of age in Japan

Product Code / Study Number:	SP0047 / EFC16335_MEQ00068
Development Phase:	Phase III
Sponsor:	Sanofi K.K.
	3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1488, Japan
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular
Indication For This Study:	MenACYW conjugate vaccine as a single dose in children, adolescents and adults 2 to 55 years of age
Manufacturer:	Sanofi Pasteur Inc.
	Discovery Drive, Swiftwater, PA 18370-0187, USA

Version Number:	1.0	**EudraCT:**	Not applicable
		IND Number(s):	Not applicable
		WHO universal trial number:	U1111-1241-8382
Date:	10-Mar-2020	Total number of pages:	86

NAMES AND ADDRESSES OF

INVESTIGATORS	Name: Address: Tel: Fax: E-mail:	This is a multi-center study with multiple Investigators. Investigators and study sites are listed in the list of Investigators and centers involved in the study.
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendement	Date, version
Clinical Study Protocol		05-Dec-2019, version 1.0 (electronic 1.0)

OVERALL RATIONALE FOR THE AMENDMENT

The revisions made are owing to the PMDA requests or requirements as summarized below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3.2 Potential Risks to Subjects	Added induration as injection site reaction	As requested by PMDA
Section 5.2.5 Exclusion Criteria	Added the explanation of the contraception methods	As requested by PMDA
Section 6.7 Concomitant Medication and Other Therapies	Deleted the description that medications will not be coded	Medication will be coded for the PMDA requirements on electronic study data submission
Section 9.2.2.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 After Vaccination)	Added the terminology, definitions, and intensity scales for Injection site induration on Table 1 and Table 2	As requested by PMDA

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SYNOPSIS

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

Title of the Study:	Immunogenicity and Safety of a Single Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Children, Adolescents and Adults 2 to 55 Years of Age
Development Phase:	Phase III
Coordinating Investigator:	Not applicable
Study Sites:	This will be a multi-center study conducted at approximately 5 sites in Japan. Investigators and sites are listed in the list of Investigators and centers Involved in the study.
Planned Study Period:	22 May 2020 to 16 December 2020
Study Design, Schedule of Study Procedures, and Methodology:	This will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate immune non-inferiority of MenACYW conjugate vaccine versus Menactra® and describe the safety and additional immunogenicity of the study vaccines in children (2-9 years of age), adolescents (10-17 years of age) and adults (18-55 years of age) in Japan. Approximately 360 healthy children, adolescents and adults will be stratified and randomly assigned in a 1:1 ratio to the following groups: • Group 1 (investigational): MenACYW conjugate vaccine (180 subjects) • Group 2 (control): Menactra® (180 subjects) All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 days post-vaccination. Solicited injection site and systemic reactions will be collected for 7 days after vaccination, unsolicited adverse events (AEs) will be collected from Visit 1 (Day [D] 0) to Visit 2 (D30 [+14 days]), and serious adverse events (SAEs) will be collected from signing of the informed consent at D0 through D30 (+14 days) after vaccination. **Vaccination** All subjects will receive a single intramuscular (IM) dose of either MenACYW conjugate vaccine or Menactra® on D0. **Blood sampling** All subjects will provide a pre-vaccination blood sample at Visit 1 (D0) and a post-vaccination sample at Visit 2 (D30 [+14 days] after the vaccination at Visit 1). **Collection of safety data** • All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report form (CRF). • The subject or the subject's parent / legally acceptable representative will record information in a diary card about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from Visit 1 (D0) to Visit 2 (D30 [+14 days]). SAEs will be reported throughout the duration of the study from the signing of the

	informed consent form (ICF) or the assent form. • In addition, the subject or subject's parent / legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the study. • Study site staff will contact the subject or the subject's parent / legally acceptable representative by telephone on D8 (+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 at Visit 2. • The completed diary card will be reviewed with the subject and/or the subject's parent / legally acceptable representative at Visit 2.
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 IRBs, or the governing regulatory authority in Japan where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authority, 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 or subjects' parents / legally acceptable representatives and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine compared with those observed following the administration of a single dose of Menactra®
Primary Endpoint:	Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at baseline (Visit 1, D0, before vaccination) and at Visit 2 (D30 [+14 days]) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra® (Group 1 versus Group 2)
Secondary Objectives:	**Immunogenicity** To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra® **Safety** To describe the safety profile of MenACYW conjugate vaccine and that of Menactra®
Secondary Endpoints:	**Immunogenicity** Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and after vaccination at D30 (+14 days) for all groups • hSBA vaccine seroresponse • Proportion of subjects with hSBA titer ≥1:4 and ≥1:8 • hSBA geometric mean titer (GMT) • hSBA titer distribution and reverse cumulative distribution curve (RCDC) • Proportion of subjects with hSBA titer ≥4-fold rise from baseline (Visit 1, D0, before vaccination) to after vaccination (Visit 2, D30 [+14 days]) **Safety** • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination, of any

	unsolicited systemic AEs reported in the 30 minutes after vaccination. • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) injection site reactions occurring up to 7 days after vaccination. • Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) systemic reactions occurring up to 7 days after vaccination. • Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to Visit 2 after vaccination. • Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the study from Visit 1 (D0) to Visit 2 (D30 [+14 days]) after vaccination.
Planned Sample Size:	A total of 360 subjects are planned to be enrolled: • Group 1 (investigational): MenACYW conjugate vaccine (n=180) • Group 2 (control): Menactra® (n=180) [redacted]
Duration of Participation in the Study:	The duration of each subject's participation in the study will be approximately 30 to 44 days.
Investigational Product:	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
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 µg Serogroup C……10 µg Serogroup Y……10 µg Serogroup W……10 µg Tetanus toxoid protein carrier……..approximately 55 µg
Route:	IM
Batch Number:	To be determined
Control Product:	**Menactra®**: Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
Form:	Liquid solution for injection

Composition:	Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain as active ingredients the following meningococcal capsular polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein: Serogroup A……4 µg Serogroup C……4 µg Serogroup Y……4 µg Serogroup W-135……4 µg Diphtheria toxoid protein carrier……approximately 48 µg
Route:	IM
Batch Number:	To be determined
Inclusion Criteria:	An individual must fulfill all of the following criteria to be eligible for study enrollment: I 01. Aged 2 to 55 years on the day of inclusion I 02. Informed consent form has been signed and dated by the subjects or subjects' parents / legally acceptable representatives as applicable In addition: Subjects 7 to 19 years will provide written assent I 03. Subjects (and subjects' parents / legally acceptable representatives for the 2 to 19 years age groups) are able to attend all scheduled visits and to comply with all study procedures
Exclusion Criteria:	An individual fulfilling any of the following criteria is to be excluded from study enrollment: E 01. Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination) E 02. Participation in the 4 weeks preceding the study vaccination or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure E 03. Receipt of any vaccine in the 4 weeks preceding the study vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after the study investigational vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines E 04. Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B vaccine) E 05. Receipt of immune globulins, blood or blood-derived products in the past 3 months E 06. 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) E 07. History of meningococcal infection, confirmed either clinically, serologically, or microbiologically E 08. At high risk for meningococcal infection during the study (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease)

	E 09. Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances E 10. Laboratory confirmed / self-reported thrombocytopenia, contraindicating intramuscular vaccination in the Investigator's judgment E 11. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's judgement E 12. History of Guillain-Barre syndrome (GBS) E 13. History of convulsions E 14. History of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine and a diphtheria toxoid-containing vaccine within 10 years of the proposed study vaccination E 15. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily E 16. Current alcohol abuse or drug addiction E 17. Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion E 18. Moderate or severe acute illness/infection (according to Investigator judgment) or febrile illness (temperature ≥99.5°F or ≥37.5°C) on the day of vaccination. A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided E 19. Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw E 20. Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
Statistical Methods:	All immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set (FAS) according to randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS). **Primary Objective** Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse. Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the percentage of subjects who achieve an hSBA vaccine seroresponse* for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2. Null hypothesis (H0): $p_{(G1)} - p_{(G2)} \leq -10\%$ Alternative hypothesis (H1): $p_{(G1)} - p_{(G2)} > -10\%$ where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse in Group 1 and Group 2, respectively. Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is >−10%, the inferiority assumption will be rejected. * Vaccine seroresponse for serogroups A, C, Y, and W is defined as post-vaccination hSBA titers ≥1:16 for subjects with pre-vaccination hSBA titers <1:8 or at least a 4-fold increase in hSBA titers from pre- to post-vaccination for subjects with pre-vaccination hSBA titers ≥1:8.

Secondary Objectives

Immunogenicity

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in each lot of MenACYW conjugate vaccine and Menactra®.

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

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

- hSBA vaccine seroresponse rate and 95% CI
- Proportion of subjects with hSBA titer ≥1:4 and ≥1:8 and 95% CI
- hSBA GMT and 95% CI
- hSBA titer distribution and RCDCs
- Proportion of subjects with hSBA titer ≥4-fold rise from baseline (Visit 1, D0, before vaccination) to after vaccination (Visit 2, D30 [+14 days]) and 95% CI

Safety

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

Calculations of Sample Size

A total of 360 subjects (180 subjects per group) will be enrolled and randomly assigned to treatment.

[redacted]

Power of the study based on the primary objective of non-inferiority with [redacted] evaluable subjects per group

Serogroup	Estimated[a] MenACYW conjugate vaccine	Estimated[b] Menactra®	Non-inferiority margin	Power
[redacted]				

[redacted]

TABLE OF STUDY PROCEDURES

Phase III Study, 2 Visits, 1 Vaccination, 2 Blood Samples, 1 Telephone Call, 30 to 44 Days Duration Per Subject

Visit / Contact	Visit 1	Telephone Call 1	Visit 2
Study timelines (days)	Day 0	Day 8	Day 30
Time windows (days)	--	+2 days	+14 days
Informed consent form / assent form (if applicable)	X		
Inclusion / exclusion criteria	X		
Collection of demographic data	X		
Urine pregnancy test (if applicable)	X		
Medical history	X		
Physical examination[a]	X		
Review of temporary contraindications for blood sampling[b]			X
Contact interactive response technology (IRT)	X		X
Randomization / allocation	X		
Blood sampling (BL), 5 mL	BL0001[c]		BL0002
Vaccination[d]	X		
Immediate surveillance (30 min)	X		
Diary card provided	X		
Telephone call		X[e]	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited AEs	D0 to Visit 2		
Diary card reviewed and collected			X
Reporting of SAEs	To be reported at any time during the study		
Collection of reportable concomitant medications	X		X
Termination of study			X

a Physical examination can be done in accordance with medical practice at each site and for each age range. Body temperature (preferably axillary temperature) will be measured and recorded in source documents.

b Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0), when possible.

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

d Subjects will receive 1 dose of MenACYW conjugate vaccine or Menactra®.

e This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the study site staff will find out whether the subject experienced any SAE not yet reported, and will remind the subject or subject's parent / legally acceptable representative to continue using the diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2.

LIST OF ABBREVIATIONS

AE	adverse event
AR	adverse reaction
BL	blood sampling
CDM	Clinical Data Management
CI	confidence interval
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	case report form
D	day
EDC	electronic data capture
FAS	Full Analysis Set
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barre syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GDPR	Global Data Protection Regulation
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global Pharmacovigilance
hSBA	serum bactericidal assay using human complement
IASR	Infectious Agents Surveillance Report
IATA	International Air Transport Association
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IMD	invasive meningococcal disease
IME	important medical event
IOM	Institute of Medicine
IP	investigational product
IRB	Institutional Review Board

IRT	interactive response technology
LCLS	last contact, last subject
LLOQ	lower limit of quantification
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
µg	micrograms
mL	milliliter
N.	*Neisseria*
NSAID	non-steroidal anti-inflammatory drug
PPAS	Per-Protocol Analysis Set
RCDC	reverse cumulative distribution curve
PMDA	Pharmaceuticals and Medical Device Agency
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SAP	statistical analysis plan
SMM	Study Medical Manager
SafAS	Safety Analysis Set
ULOQ	upper limit of quantitation
USA	United States of America

1 INTRODUCTION

1.1 BACKGROUND

This trial will evaluate the immune non-inferiority of MenACYW conjugate vaccine versus Menactra®, and will describe the safety and immunogenicity of MenACYW conjugate vaccine and Menactra® in children, adolescents, and adults 2 to 55 years of age in Japan.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria* (*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. 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 (5) (6) (7) and more recently in Chile (8), Turkey (9) (10), China (11), Argentina (12), and Brazil (13) (14), 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 (9) (15). Serogroup Y has not been associated with outbreaks, but its frequency as a cause of sporadic cases has gradually increased in the United States of America (USA) and more recently in Canada and Europe (16) (17) (18). This serogroup is commonly associated with meningococcal pneumonia, particularly in older adults >65 years of age (19). Outbreaks of serogroup B meningococcal disease have also been reported on college campuses in the USA: 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 (20) (21).

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 (22).The highest proportion of meningococcal cases was due to serogroup B in the population under 5 years of age. The highest proportion of serogroup C cases was observed in the population 25 to 44 years of age while the proportion of serogroup Y cases was highest in the population age 65 years and above.

Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in 2013-2014 compared with an average of 1% to 2% of all IMD cases in earlier years (23). A gradual increase in serogroup Y IMD has also been recently reported in Sweden during 2005-2012 (24) (25). Nearly 50% of all IMD was caused by serogroup Y in 2012 (24). Similarly, an increase in the

proportion of IMD caused by serogroup Y has been observed in other Scandinavian countries, accounting for 31% in Norway in 2009-2010 and 38% in Finland in 2010 (26).

In the USA, the incidence rate of IMD was 0.14 per 100 000 in all ages; 0.83 per 100 000 in infants less than 1 year; 0.62 per 100 000 in toddlers 1 year of age; 0.27 per 100 000 in children 2 to 4 years of age; and 0.02 per 100 000 in children 5 to 17 years of age in 2013. The age-specific incidence rate per 100 000 was 0.08 in adults 50 to 64 years of age, 0.03 in adults 65 to 74 years of age, 0.14 in adults 75 to 84 years of age, and 0.43 in adults 85 years of age and older in 2013 (27).

The epidemiological trend of IMD in Japan is described below based on Infectious Agents Surveillance Report (IASR) published by Infectious Disease Surveillance Center, National Institute of Infectious Diseases in January 2018 (28).

Invasive meningococcal infection in Japan: A total of 160 cases were notified in Japan from April 2013 to October 2017 as epidemiological trend.

Gender and age distribution: Among the 160 cases reported from April 2013 to October 2017, the male-to-female ratio was about 3:2, and many cases were those aged 0-4 years, 15-19 years, and those in their 40s to early 70s. Among invasive meningococcal infection cases, reported as such since 2013, the case-fatality rate at the time of notification was 15.0% (24/160). Based on the information at the time of notification, two thirds of the reported deaths were among those aged in their 10s to 50s.

Serogroup distribution: From April 2013 to October 2017, there were 160 reported cases of invasive meningococcal infection, and among them, serogroup information was obtained from 116 (72.5%) cases. Serogroup Y was the most frequent serogroup (75 cases), followed by serogroup B (15 cases), serogroup C (13 cases) and serogroup W (5 cases). In addition, there were 4 cases that could not be distinguished between serogroup Y and W and 4 non-typable strain cases. In the past, serogroup B was considered to be predominant but recently serogroup Y is dominant in Japan. Indeed, it occurs in 20 to 40 people, and Y is the largest as serogroup.

The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, Y, and W in all target age groups.

1.2 BACKGROUND OF THE INVESTIGATIONAL PRODUCT

1.2.1 Non-clinical Safety

MenACYW conjugate vaccine has been evaluated for toxicity in rats and for the ability to elicit polysaccharide-specific antibody (total and bactericidal antibodies) responses in mice and rats. These species generate only marginal antibody responses to polysaccharides alone but strong responses to polysaccharides conjugated to a carrier protein.

MenACYW conjugate vaccine was well tolerated in rats administered 4 intramuscular (IM) injections of MenACYW conjugate vaccine at 10 micrograms (µg) per serogroup, which

corresponds to the human dose level. The non-clinical safety data for MenACYW conjugate vaccine showed no major safety concerns and support the use of MenACYW conjugate vaccine in future clinical trials with the same formulation.

1.2.2 Clinical

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

Based on the information from 12 completed clinical trials, overall, a total of 11,538 participants have been enrolled and vaccinated, of which approximately 7613 have received MenACYW conjugate vaccine (different formulations). Subjects received single (n=7006; 92.0%) or multiple doses (n=607; 8.0%) of MenACYW conjugate vaccine given alone (n=6026; 79.2%) or with at least one concomitant vaccine (n=1587; 20.8%).

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.

1.2.2.1 Study MET35 (Phase III)

MET35 was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to a licensed quadrivalent meningococcal conjugate vaccine in healthy children 2 to 9 years of age in the USA and Puerto Rico.

A total of 1000 meningococcal-vaccine naïve children were randomized to the following groups:

- Group 1: MenACYW conjugate vaccine
- Group 2: MENVEO®

Immunogenicity

Non-Inferiority of MenACYW Conjugate Vaccine to MENVEO®

The immune response following administration of MenACYW conjugate vaccine was non inferior to the immune response following administration of MENVEO® for all 4 serogroups as measured by serum bactericidal assay using human complement (hSBA) vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% confidence interval (CI) of the difference was greater than -10%.

hSBA Vaccine titers ≥1:8 at Day (D) 30

Thirty days after vaccination, the percentages of subjects with hSBA titers ≥1:8 were increased from baseline for all serogroups and both groups. Percentages of subjects with hSBA titers ≥1:8 were numerically higher in Group 1 (86.4%) than in Group 2 (79.3%), with overlapping CIs, for

serogroup A, and were higher in Group 1 than in Group 2, with non-overlapping CIs for serogroups C, Y, and W.

Antibody Responses (hSBA geometric mean titers [GMTs]) at D30

At D30, the Group 1 / Group 2 GMT ratios ranged from 1.09 to 14.0 for all serogroups.

Antibody Responses (hSBA GMTs) at D30 by Age Group

At D30, the Group 1 / Group 2 geometric mean titer ratios (GMTRs) ranged from 1.14 to 17.4 in subjects aged 2 to 5 years and from 1.06 to 11.5 in subjects aged 6 to 9 years for all serogroups.

In subjects aged 2 to 5 years, at D30, the GMTs in Group 1 were numerically higher than in Group 2 for serogroups A and Y (21.6 and 49.8 in Group 1 and 18.9 and 36.1 in Group 2, respectively) with overlapping 95% CIs, and the GMTRs for serogroups A and Y were 1.14 and 1.38, respectively. The GMTs were higher in Group 1 than in Group 2 for serogroups C and W (208 and 28.8 in Group 1 and 11.9 and 20.1 in Group 2, respectively) with non-overlapping 95% CIs; and the GMTRs for serogroups C and W were 17.4 and 1.43, respectively.

In subjects aged 6 to 9 years, at D30, the GMTs were numerically higher in Group 1 (28.4) than in Group 2 (26.8) for serogroup A with overlapping 95% CIs, and the GMTR was 1.06. The GMTs were higher in Group 1 than in Group 2 with non-overlapping 95% CIs for serogroups C, Y, and W ranging from 48.9 to 272 in Group 1 and from 23.7 to 51.8 in Group 2, and GMTRs ranging from 1.45 to 11.5.

Safety

The safety objective of the study was to describe the safety profile of MenACYW conjugate vaccine compared to that of the licensed Menveo®. Overall, vaccination with MenACYW conjugate vaccine among children aged 2 to 9 years was found to be safe, with no safety concerns identified. The safety profile was comparable in subjects from the age subgroup 2 to 5 years and subjects from the age subgroup 6 to 9 years between both treatment groups (Group 1 and Group 2). The MenACYW conjugate vaccine was well tolerated with no immediate hypersensitivity reactions, no discontinuations due to a serious adverse event (SAE) or other adverse event (AE), and no related SAEs.

The majority of reactions at the MenACYW conjugate vaccine or MENVEO® injection sites were of Grade 1 or 2 intensity, started between D0 and D03, and lasted 1 to 3 days. Grade 3 Erythema and swelling were reported at a lower frequency in MenACYW conjugate vaccine Group (3.1% and 1.4%, respectively) than in Menactra® Group (9.9% and 5.6%, respectively). Overall, most solicited systemic reactions were of Grade 1 or Grade 2 intensity, started between D0 and D30, and lasted 1 to 3 days.

Three subjects experienced SAEs within the first 30 days after vaccination. Seven subjects (5 in Group 1 and 2 in Group 2) experienced a total of 9 SAEs after D30 through the 6-month follow-up. None of the SAEs were considered as related to the vaccine by the Investigator and

none led to discontinuation from the study. No cases of death were reported during the study. No pregnancies were reported during the study.

Overall, the safety profile of MenACYW conjugate vaccine was comparable to that of the licensed vaccine, Menveo®.

1.2.2.2 Study MET43 (Phase III)

MET43 was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate immune lot consistency of MenACYW conjugate vaccine, evaluate the immune non-inferiority versus Menactra®, and describe the safety and additional immunogenicity of these study vaccines in adolescents and adults aged 10 to 55 years in the USA.

A total of 3344 healthy, meningococcal-vaccine naïve adolescents and adults were randomized in a 3:3:3:2 ratio to the following groups:

- Group 1: MenACYW conjugate vaccine (Lot 1)
  - Group 1a: 400 subjects 10 to 17 years of age
  - Group 1b: 500 subjects 18 to 55 years of age
- Group 2: MenACYW conjugate vaccine (Lot 2)
  - Group 2a: 400 subjects 10 to 17 years of age
  - Group 2b: 500 subjects 18 to 55 years of age
- Group 3: MenACYW conjugate vaccine (Lot 3)
  - Group 3a: 400 subjects 10 to 17 years of age
  - Group 3b: 500 subjects 18 to 55 years of age
- Group 4: Menactra®
  - Group 4a: 300 subjects 10 to 17 years of age
  - Group 4b: 300 subjects 18 to 55 years of age

Immunogenicity

Equivalence of 3 MenACYW conjugate vaccine lots in terms of GMTs

Immune equivalence was demonstrated across the 3 lots in that the 2-sided 95% CI of the ratio of the GMTs was between >1/2 and <2 for each pair of lots and each serogroup.

Non-Inferiority of MenACYW Conjugate Vaccine to Menactra®

Non-inferiority of immune response was demonstrated between MenACYW conjugate vaccine and Menactra® based on percentage of subjects achieving hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was >−10%. The percentage of subjects with an hSBA vaccine seroresponse was numerically higher in Groups 1-3 pooled than in

Group 4 for all serogroups: ranging from 73.8% (1846/2503) to 91.4% (2290/2505) in Groups 1-3 pooled and from 47.9% (284/593) to 73.4% (435/593) in Group 4.

Antibody Responses (hSBA Titers ≥1:8) at D30

Thirty days after vaccination, the percentages of subjects with hSBA titers ≥1:8 were increased from baseline for all serogroups and all groups. Percentages of subjects with hSBA titers ≥1:8 after MenACYW conjugate vaccine were similar in Group 1, Group 2 and Group 3. In Groups 1-3 pooled, the percentages ranged from 94.7% to 98.8%. In Group 4, the percentages of subjects with hSBA titers ≥1:8 after Menactra® tended to be numerically lower ranging from 76.2% to 88.5%.

Antibody Responses (hSBA GMTs) at D30

At D30, the Group 1-3 pooled / Group 4 GMT ratios ranged from 1.90 to 8.05 for all serogroups.

Antibody Responses (serum bactericidal assay using baby rabbit complement [rSBA] GMTs and seroresponse) at D30

At D30, meningococcal rSBA GMTs for all serogroups were higher after MenACYW conjugate vaccine than after Menactra® for all serogroups. The percentages of subjects with an rSBA vaccine seroresponse was comparable in all groups for serogroups A and W but were numerically higher after vaccination with MenACYW conjugate vaccine than after vaccination with Menactra® for serogroups C and Y.

Safety

The safety objective of the study was to describe the safety profile of MenACYW conjugate vaccine compared to that of the licensed Menactra®.

Vaccination with MenACYW conjugate vaccine among adolescents and adults aged 10 to 55 years was found to be safe, with no safety concerns identified, and no discontinuations due to an SAE or other AE, and no related SAEs.

The majority of reactions at the MenACYW conjugate vaccine or Menactra® injection sites were of Grade 1 or Grade 2 intensity, started between D0 and D03, and most lasted 1 to 3 days. The injection site reactions were reported at similar frequencies in all groups with pain being the most frequently reported injection site reaction. Overall, most solicited systemic reactions were of Grade 1 or Grade 2 intensity, started between D0 and D03, and most lasted 1 to 3 days.

Few subjects reported immediate unsolicited AEs: 0.3% (3/895) of subjects in Group 1, 0.5% (4/883) of subjects in Group 2, 0.3% (3/898) of subjects in Group 3, 0.4% (10/2676) of subjects in Groups 1-3 pooled, and 0.5% (3/635) of subjects in Group 4. There were no immediate SAEs, including any anaphylactic or life-threatening events. Most unsolicited non-serious AEs within 30 days of vaccine injection were of Grade 1 or Grade 2 intensity.

Five subjects experienced SAEs within the first 30 days after vaccination. Twenty-eight subjects experienced a total of 34 SAEs after D30 through the 6-month follow-up. None of the SAEs were considered as related to the vaccine by the Investigator and none led to discontinuation from the

study. No cases of death were reported during the study. There were 13 reported pregnancies during the study: 5 in Group 1, 5 in Group 2, 1 in Group 3, and 2 in Group 4. Of these pregnancies, 1 was classified as exposed and pregnant at time of vaccination with MenACWY conjugate vaccine whereas urine pregnancy test was negative on vaccination day, 8 were classified as unexposed, and 4 as exposed but not yet pregnant. The pregnancy outcome was known for the 11 subjects who were administered MenACYW conjugate vaccine and 1 of the 2 subjects that were administered Menactra®. Ten subjects gave birth to healthy babies, 2 reports were of spontaneous abortion (subjects had received MenACYW conjugate vaccine; both pregnancies were classified as unexposed; and none were considered as related to the vaccine by the Investigator), and 1 pregnancy was lost to follow-up.

Overall, the safety profile of MenACYW conjugate vaccine was comparable to that of the licensed vaccine, Menactra®.

1.2.2.3 Study MET49 (Phase III)

MET49 was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® – A/C/Y/W-135 in adults ≥56 years of age in the USA.

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

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

Immunogenicity

Non-Inferiority of MenACYW Conjugate Vaccine to Menumone®

The immune response following administration of a single dose of MenACYW conjugate vaccine was non-inferior to the immune response following administration of a single dose of Menomune® − A/C/Y/W-135 for all 4 serogroups as measured by hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was more than −10%.

Antibody Responses (hSBA Titers ≥1:8) at D30

Thirty days after vaccination, the percentages of subjects with hSBA titers ≥1:8 increased from baseline for all serogroups and in both groups. The percentages were comparable for serogroup A between Group 1 (89.4%) and Group 2 (84.2%). For serogroups C, Y, and W, the percentages were higher in Group 1 than Group 2 with non-overlapping 95% CIs (90.1% vs 71.0%, 91.7% vs 67.7%, and 77.4% vs 63.1%, in Group 1 vs Group 2 respectively).

Antibody Responses (hSBA GMTs) at D30

At D30, the Group 1 / Group 2 GMT ratios ranged from 1.75 to 4.10 for all serogroups.

Antibody Responses (rSBA GMTs and seroresponse) at D30

At D30, meningococcal rSBA GMTs for all serogroups were higher after MenACYW conjugate vaccine than after Menomune®. The percentages of subjects with an rSBA vaccine seroresponse after vaccination with MenACYW conjugate vaccine were numerically higher than the percentages after Menomune®.

Safety

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

Overall, vaccination with MenACYW conjugate vaccine was found to be safe, with no safety concerns identified. The MenACYW conjugate vaccine was well tolerated with no discontinuations due to an SAE or other AE.

The majority of reactions at the MenACYW conjugate vaccine or Menomune® − A/C/Y/W-135 injection sites were of Grade 1 or 2 intensity, started between D0 and D03, and lasted 1 to 3 days. Erythema and swelling were reported at higher frequency in the MenACYW conjugate vaccine (5.2% and 4.5% respectively) than in the Menomune® − A/C/Y/W-135 (no subjects reported erythema or swelling). Overall, most solicited systemic reactions in both groups were of Grade 1 or 2 intensity, started between D0 and D03, and lasted 1 to 3 days.

One subject (0.2%) in Group 1 and no subjects (0.0%) in Group 2 reported 1 immediate unsolicited AE. Most unsolicited non-serious AEs within 30 days of vaccine injection were of Grade 1 or Grade 2 intensity.

Six subjects (3 subjects in each group) experienced at least one SAE within the first 30 days after vaccination on D0. Twenty-five subjects (12 in Group 1 and 13 in Group 2) experienced at least one SAE through the 6-month follow-up, for a total of 33 SAEs after: 12 subjects (2.7%) in Group 1 experienced 16 SAEs and 13 subjects (2.9%) in Group 2 experienced 17 SAEs. None of the SAEs were considered as related to the vaccine by both the Investigator and the Sponsor. There were 2 deaths reported during the study. Both subjects had been vaccinated with Menomune® − A/C/Y/W-135. None of the deaths were considered related to vaccination. No pregnancies were reported during the study.

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

1.3 POTENTIAL BENEFITS AND RISKS

1.3.1 Potential Benefits to Subjects

MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. There may be no direct benefit from receiving MenACYW conjugate vaccine.

However, based on the data generated from previous studies, the immunogenicity profile of 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 MenACYW conjugate vaccine in humans.

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

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

1.3.2 Potential Risks to Subjects

Like other vaccines, vaccination with MenACYW conjugate vaccine or Menactra® may cause injection site reactions such as pain, swelling, induration, and erythema, or certain systemic events such as fever, headache, malaise, or myalgia.

Other common reactions after Menactra® in the studied age group include injection site induration, fatigue, arthralgia, appetite lost, and diarrhea.

There may be a rare possibility of an allergic reaction which could be severe. Prior to any vaccine injection, all known precautions should be taken to prevent hypersensitivity reactions. This includes a review of the subject's prior vaccination history with respect to possible hypersensitivity to the vaccine or similar vaccines. Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be available to treat unexpected reactions (e.g., anaphylaxis).

There may also be a risk of febrile convulsion in some children who experience high fever.

There may be other risks for MenACYW conjugate vaccine which are not yet known.

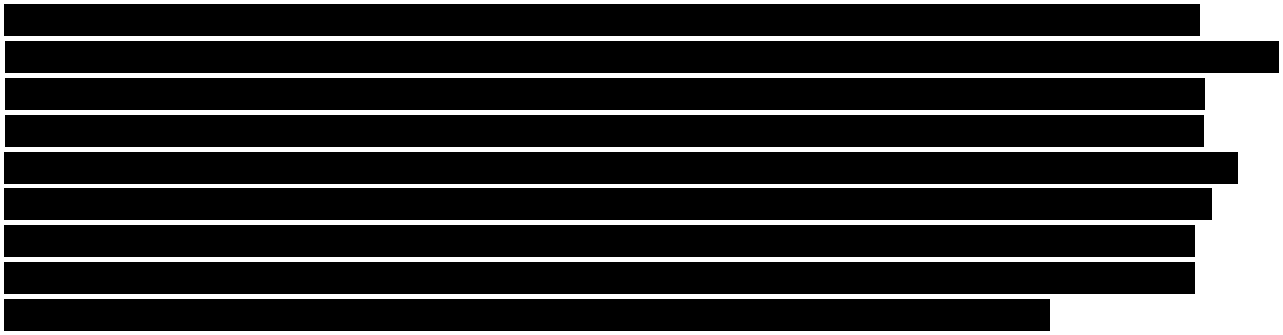
The following additional adverse events have been very rarely reported during post-approval use of Menactra®: Guillain-Barré syndrome (GBS), transverse myelitis, acute disseminated encephalomyelitis, vasovagal syncope, facial palsy, dizziness, paraesthesia, convulsion, and hypersensitivity reactions such as anaphylactic / anaphylactoid reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, and hypotension. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to Menactra® exposure.

GBS has been reported mostly in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of Menactra® (29). A retrospective cohort study carried out in the USA using healthcare claims data found no evidence of increased GBS risk following Menactra® vaccination. The study was able to exclude all but relatively small incremental risks (30).

A review by the Institute of Medicine (IOM) found inadequate evidence to accept or reject a causal relationship between tetanus toxoid-containing vaccines and GBS (31). The IOM found

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

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



The risk of vasovagal syncope exists after any vaccination in the adolescent age group. A few cases of immediate vasovagal-like response or syncope have been observed in adolescent subjects who had received MenACYW conjugate vaccine. Syncope has been reported following vaccination with Menactra®. Procedures should be in place to prevent falling injury and manage syncopal reactions.

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

The potential risk listed here are not exhaustive. Refer to the package insert of Menactra® (34) and the Investigator's brochure (IB) for the investigational vaccine for additional information regarding the potential risks.

1.4 RATIONALE FOR THE STUDY

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

Meningococcal polysaccharide vaccines have two important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) polysaccharides alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of polysaccharide vaccines in infants and children has been shown to be improved by conjugating the polysaccharides to protein carriers. Among the key advantages expected of the tetanus carrier

is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of polysaccharide-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET28 and MET32) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials.

The purpose of this trial is to evaluate the immune non-inferiority of MenACYW conjugate vaccine versus Menactra®, and describe the safety and additional immunogenicity of MenACYW conjugate vaccine and Menactra® in children, adolescents, and adults 2 to 55 years of age in Japan.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE(S)

To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine compared with those observed following the administration of a single dose of Menactra®.

The endpoint for the primary objective is presented in Section 9.1.

2.2 SECONDARY OBJECTIVE(S)

Immunogenicity

To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Menactra®.

Safety

To describe the safety profile of MenACYW conjugate vaccine and that of Menactra®.

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

3 INVESTIGATORS AND STUDY ORGANIZATION

This study will be conducted in approximately 5 centers in Japan. Details of the study centers, the Investigators at each center are provided in the list of Investigators and centers involved in the study.

Sanofi Pasteur's laboratory (Global Clinical Immunology [GCI], Swiftwater, PA, USA) or an external testing laboratory under GCI responsibility will be used for the assessment of all immunogenicity endpoints.

The Sponsor's Study Medical Manager (the SMM, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted].

4 INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Sponsor must submit this clinical study protocol to the Health Authorities (Competent Regulatory Authority) and the appropriate Institutional Review Board (IRB) / Independent Ethics Committee (IEC), and is required to forward to the respective other party a copy of the written and dated approval / favorable opinion signed by the chairman with IRB/IEC composition.

The clinical study (study number, clinical study protocol title and version number), the documents reviewed (clinical study protocol, informed consent form [ICF], IB, Investigator's curriculum vitae etc.) and the date of the review should be clearly stated on the written IRB/IEC approval / favorable opinion.

The investigational product (IP) will not be released at the study site and the Investigator will not start the study before the written and dated approval / favorable opinion is received by the Investigator and the Sponsor.

During the clinical study, any amendment or modification to the clinical study protocol should be submitted to the Health Authorities (Competent Regulatory Authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the Health Authorities (Competent Regulatory Authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study, in particular any change in safety. All updates to the IB will be sent to the IRB/IEC and to Health Authorities (Competent Regulatory Authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the study's outcome at the end of the clinical study.

5 INVESTIGATIONAL PLAN

5.1 DESCRIPTION OF THE OVERALL STUDY DESIGN AND PLAN

5.1.1 Study Design

This will be a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate immune non-inferiority of MenACYW conjugate vaccine versus Menactra® and describe the safety and additional immunogenicity of the study vaccines in children (2-9 years of age), adolescents (10-17 years of age) and adults (18-55 years of age) in Japan. Approximately 360 healthy children, adolescents and adults will be stratified and randomly assigned in a 1:1 ratio to the following groups:

- Group 1 (investigational): MenACYW conjugate vaccine (180 subjects)
- Group 2 (control): Menactra® (180 subjects)

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

Solicited injection site and systemic reactions will be collected for 7 days after vaccination, unsolicited AEs will be collected from Visit 1 (D0) to Visit 2 (D30 [+14 days]), and SAEs will be collected from signing of the informed consent at D0 through D30 (+14 days) after vaccination.

5.1.2 Justification of the Study Design

This trial is part of the ongoing development program that focuses on demonstrating that MenACYW conjugate vaccine is non-inferior to the licensed quadrivalent meningococcal conjugate vaccine in direct comparison trials. This is a study that will be conducted as part of the Phase III development of MenACYW conjugate vaccine in which the vaccine candidate will be evaluated in children, adolescents, and adults 2 to 55 years of age in Japan.

This trial is designed to evaluate the immune non-inferiority of MenACYW conjugate vaccine versus Menactra®, and will describe the safety and immunogenicity of MenACYW conjugate vaccine and Menactra® in children, adolescents, and adults 2 to 55 years of age in Japan.

This trial will be conducted in a modified double-blind method, in which only designated staff members at each study site will know which vaccine has been administered to the subjects. The subjects and the Investigator in charge of the safety assessment will be blinded in order to decrease the potential bias in safety assessments. The vaccines are prepared by the unblinded site staff member (a designated administrator such as a subinvestigator, a nurse, or a designated pharmacist) and administered by the administrator without the presence of any other site staff members who may be an assessor for safety in subsequent visits. The subjects and subjects' parents / legally acceptable representatives will also remain blinded to study product. Furthermore,

the Sponsor and laboratory personnel performing the serology testing will also remain blinded to treatment assignments throughout the trial until database lock.

5.1.3 Study Plan

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

Vaccination

All subjects will receive a single IM dose of either MenACYW conjugate vaccine or Menactra® on D0.

Blood sampling

All subjects will provide a pre-vaccination blood sample at Visit 1 D0 and a post-vaccination sample at Visit 2 (D30 [+14 days] after the vaccination at Visit 1).

Collection of safety data

- All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report form (CRF).
- The subject or the subject's parent / legally acceptable representative will record information in a diary card about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from Visit 1 (D0) to Visit 2 (D30 [+14 days]). SAEs will be reported throughout the duration of the study from the signing of the ICF or the assent form.
- In addition, the subject or subject's parent / legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the study.
- Study site staff will contact the subject or the subject's parent / legally acceptable representative by telephone on D8 (+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 at Visit 2.
- The completed diary card will be reviewed with the subject and/or the subject's parent / legally acceptable representative at Visit 2.

5.1.4 Visit Procedures

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

<u>Visit 1 (D0): Inclusion, Randomization, Blood Sample, and Vaccination</u>

1. Give the subject and/or the subject's parent / legally acceptable representative information about the study, answer any questions, obtain written informed consent and assent (as applicable) and give the subject or subject's parent / legally acceptable representative a signed copy of the ICF and a signed copy of the assent form (as applicable).

- Subjects 2 to 6 years of age: ICF signed by the subject's parent / legally acceptable representative
- Subjects 7 to 19 years of age: assent form signed by the subject and ICF signed by the subject's parent / legally acceptable representative
- Subjects 20 to 55 years of age: ICF signed by the subject

2. Check inclusion and exclusion criteria for eligibility (see Section 5.2.4 and Section 5.2.5, respectively).
3. Collect relevant demographic information.
4. Perform urine pregnancy test (if applicable).
5. Obtain verbal medical history about the subject.
6. Conduct a history-directed physical examination, including temperature (preferably axillary temperature). A physical examination conducted during the same day as part of routine clinical care may be used for this purpose.
7. Contact the interactive response technology (IRT) for subject identification number and vaccine dose number (see Section 6.5 for instructions).
8. Obtain the first blood sample (5 milliliter [mL]) (see Section 7 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (no more than 3 attempts), then Visit 1 can be rescheduled to a later date at which point informed consent and inclusion/exclusion criteria must be re-validated. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.
9. Administer the appropriate study vaccine to the subject in the deltoid muscle. The vaccine must be administered on the side opposite to that of the blood sampling.
   Note: The study product is prepared by an unblinded study site staff (a designated administrator such as a Sub-investigator or nurse, or a designated pharmacist) and administered by the administrator without the presence of any other study site staffs who may be an assessor for safety in subsequent visits. The subjects and subjects' parents / legally acceptable representatives are blinded with eye mask or other appropriate methods during administration.
10. Observe the subject for 30 minutes, and record any AE in the source document.
11. Give the subject or the subject's parent / legally acceptable representative a diary card, a thermometer, and a ruler, and go over the instructions for their use.
12. Remind the subject or the subject's parent / legally acceptable representative to expect a telephone call 8 days (+2 days) after Visit 1 and to bring back the diary card when they return for Visit 2 at a specified date and time.
13. Remind the subject or the subject's parent / legally acceptable representative to notify the site in case of an SAE.
14. Complete the relevant CRF pages for this visit.

Telephone Call 1 (D8 [+2 days] after Visit 1)

Note: If D8 falls on a weekend or a holiday, the telephone call may be made on the following business day. If the subject or the subject's parent / legally acceptable representative is not available, the study site staff should document the attempts to make contact.

1. Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2. Remind the subject or the subject's parent / legally acceptable representative to do the following:
   - Complete the D0 to D7 pages 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 (D30 [+14 days] after Visit 1): Collection of Safety Information and Blood Sample

1. Review the pages of the diary card with the subject or the subject's parent / legally acceptable representative, including any AEs, medications, or therapy that occurred since vaccination.
2. Review the temporary contraindications for blood sampling (see Section 5.2.8).
3. Obtain the second blood sample (see Section 7 for detailed instructions regarding the handling of blood samples).
4. Complete the termination record of the CRF.
5. If the subject does not return for Visit 2, and the diary card is not received at the site, study site staffs will contact the subject or the subject's parent / legally acceptable representative by telephone. During the telephone call, the subject or the subject's parent / legally acceptable representative will be reminded to return the diary card to the study site. Telephone calls will be documented on the telephone/interview record. If the study site staffs are unable to contact the subject or the subject's parent / legally acceptable representative with 3 attempts, the study site staffs will follow instructions given in Section 5.2.11.
6. Contact the IRT to inform the subject's status.

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

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

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

5.1.5 Planned Study Calendar

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

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject): 22 May 2020 to 16 December 2020

Planned inclusion period - FVFS to FVLS (first visit, last subject): 22 May 2020 to 11 November 2020

Planned vaccination period: 22 May 2020 to 11 November 2020

Planned end of study (LCLS): 16 December 2020

Planned date of final clinical study report: 26 Jun 2021

5.2 ENROLLMENT AND RETENTION OF STUDY POPULATION

5.2.1 Recruitment Procedures

Before the start of the study, the Investigator and/or study site staff may contact the subjects or the subjects' parents / legally acceptable representatives of an appropriate pool of potential subjects and invite them to participate in the study. The site will ensure that any advertisements used to recruit subjects (e.g., letters, pamphlets, and posters) are submitted to Sponsor for review prior to submission to the IRB/IEC for approval.

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

5.2.2 Informed Consent Procedures

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the subject and/or subject's parent / legally acceptable representative of all pertinent aspects of the clinical study including the written information giving approval / favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a subject's participation in the clinical study, the written ICF (and assent form) should be signed, name filled in, and personally dated by the subject and/or by subject's parent / legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF (and assent form) will be provided to the subject or subject's parent / legally acceptable representative.

The ICF (and assent form) used by the Investigator for obtaining the informed consent of the subject or subject's parent / legally acceptable representative must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval / favorable opinion.

The written ICF and any other written information to be provided to subjects or subjects' parents / legally acceptable representatives should be revised whenever important new information becomes available that may be relevant to the consent of the subject or subject's parent / legally acceptable representative. Any revised written ICF and assent form, and written information should receive the IRB/IEC's approval / favorable opinion in advance of use. The subject and/or subject's parent / legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the willingness of the subject or subject's parent / legally acceptable representative to continue participation in the study. The communication of this information should be documented. In case of study suspension due to safety concerns, subjects and/or subjects' parents / legally acceptable representatives will be informed of this study suspension and the reason for it. Once it is confirmed that it is safe for the study to continue, subjects and/or subjects' parents / legally acceptable representatives will be asked to confirm their agreement to continue the study.

5.2.3 Screening Criteria

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

5.2.4 Inclusion Criteria

An individual must fulfill all of the following criteria to be eligible for study enrollment:

I 01. Aged 2 to 55 years on the day of inclusion

I 02. Informed consent form has been signed and dated by the subjects or subjects' parents / legally acceptable representatives as applicable
In addition:
Subjects 7 to 19 years will provide written assent

I 03. Subjects (and subjects' parents / legally acceptable representatives for the 2 to 19 years age groups) are able to attend all scheduled visits and to comply with all study procedures

5.2.5 Exclusion Criteria

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

E 01. Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least

1 year, surgically sterile, or using an effective method of contraception[1] or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination)

E 02. Participation in the 4 weeks preceding the study vaccination or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

E 03. Receipt of any vaccine in the 4 weeks preceding the study vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after the study investigational vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines

E 04. Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B vaccine)

E 05. Receipt of immune globulins, blood or blood-derived products in the past 3 months

E 06. 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)

E 07. History of meningococcal infection, confirmed either clinically, serologically, or microbiologically

E 08. At high risk for meningococcal infection during the study (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease)

E 09. Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances

E 10. Laboratory confirmed / self-reported thrombocytopenia, contraindicating intramuscular vaccination in the Investigator's judgment

E 11. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's judgement

E 12. History of GBS

E 13. History of convulsions

[1] Effective methods of contraception include oral contraception (pill), intrauterine device, or condoms used with spermicide.

E 14. History of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine and a diphtheria toxoid-containing vaccine within 10 years of the proposed study vaccination

E 15. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E 16. Current alcohol abuse or drug addiction

E 17. Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion

E 18. Moderate or severe acute illness/infection (according to Investigator judgment) or febrile illness (temperature ≥99.5°F or ≥37.5°C) on the day of vaccination. A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided

E 19. Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

E 20. Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

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

5.2.6 Medical History

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

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

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

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

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

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable.

5.2.8 Contraindications for Visit 2 Blood Samples

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 (72 hours) since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this 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 and/or subjects' parents / legally acceptable representatives 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 or subject's parent's / legally acceptable representative's permission (withdrawal)
- At the request of the subject or subject's parent / legally acceptable representative (dropout)

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

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

Withdrawn subjects will not be replaced.

5.2.10 Lost to Follow-up Procedures

In the case of subjects who fail to return for Visit 2, documented reasonable effort (i.e., documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the 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 9.2.2.1.
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 or subject's parent / legally acceptable representative did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (e.g., deviation of the Inclusion/Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • The subject or the subject's parent / legally acceptable representative signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit.
Withdrawal by Subject or Subject's Parent / Legally Acceptable Representative	To be used: • When the subject or subject's parent / legally acceptable representative indicated unwillingness to continue in the study • When the subject or subject's parent / legally acceptable representative made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., subject is relocating, inform consent withdrawal, etc.)

5.2.12 Follow-up of Discontinuations

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

For subjects where the reason for early termination was lost to follow-up or if the subject or subject's parent / legally acceptable representative 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

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

All pregnancy cases should be reported if they occurred during the study. 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 site staff must then maintain contact with the subject to obtain information about the outcome (i.e., details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be provided to the Sponsor within 1 month of delivery.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, 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 Sponsor regardless of when the SAE occurs (e.g., 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 for advice on how to address any study related medical question or problem. If the Sponsor is not available, then the Investigator may contact the Call Center — available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sponsor’s contact, as needed. The toll-free contact information for the Call Center is provided in the clinical study protocol (see Names and Addresses).

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 Sponsor (see Section 10).

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

5.4 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 IRBs, or the governing regulatory authority in Japan where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authority, 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 or subjects’ parents / legally acceptable representatives and should assure appropriate subject therapy and/or follow-up.

5.5 PREMATURE CLOSE-OUT OF A SITE

5.5.1 By the sponsor

The sponsor has the right to terminate the participation of an individual site at any time, for any reason, including but not limited to the following:

- The Investigator has received from the Sponsor all IP, means, and information necessary to perform the clinical study and has not included any subject after a reasonable period of time mutually agreed upon
- Non-compliance of the Investigator or Sub-investigator, delegated site staff with any provision of the clinical study protocol, and breach of the applicable laws and regulations or breach of the ICH GCP

In any case, the Sponsor will notify the Investigator of its decision by written notice.

5.5.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical study.

In the event of premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authority should be informed according to applicable regulatory requirements.

6 PRODUCTS ADMINISTERED

6.1 IDENTITY OF THE INVESTIGATIONAL PRODUCT(S)

6.1.1 Identity of Study Product(s)

MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine

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 ingredients:

Meningococcal capsular polysaccharides:

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

Tetanus toxoid protein carrier……approximately 55 µg

6.1.1.2 Preparation and Administration

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

The study product is prepared by an unblinded study site staff (a designated administrator such as a Sub-investigator or nurse, or a designated pharmacist) and administered by the administrator without the presence of any other study site staffs who may be an assessor for safety in subsequent visits. The subjects and subjects' parents / legally acceptable representatives are blinded with eye mask or other appropriate methods during administration.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and/or discoloration,

whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor.

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

The site of IM injection should be prepared with a suitable antiseptic prior to administration of one 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 in Group 1 will receive 1 dose of MenACYW conjugate vaccine on D0.

6.1.2 Identity of Control Product(s)

Menactra®: Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

Form: Liquid solution for injection

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.1.2.1 Composition

Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain as active ingredients the following meningococcal capsular polysaccharides conjugated to approximately 48µg of diphtheria toxoid protein:

Serogroup A…….....4 µg
Serogroup C…….....4 µg
Serogroup Y…….....4 µg
Serogroup W-135……4 µg

Diphtheria toxoid protein carrier.....approximately 48 µg

6.1.2.2 Preparation and Administration

Menactra® is supplied in single-dose (0.5 mL) vials.

See the Menactra® package insert (34). The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.2.3 Dose Selection and Timing

All subjects in Group 2 will receive 1 dose of Menactra® on D0.

6.2 IDENTITY OF OTHER PRODUCT(S)

Not applicable.

6.3 PRODUCT LOGISTICS

6.3.1 Labeling and Packaging

MenACYW conjugate vaccine and a commercial lot of Menactra® will be supplied in single-dose vials, labeled and packaged according to national regulations.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Sponsor's monitoring staff 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 procedures for the product management, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sponsor representative, and request authorization from the Sponsor to use the product.

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a study site staff 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 procedures for the product

management) 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 Sponsor 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.

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

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

6.3.3 Replacement Doses

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

6.3.4 Disposal of Unused Products

Unused or wasted products will be returned to the Sponsor in accordance with the instructions in the procedures for the product management. Product accountability will be verified throughout the study period.

6.3.5 Recall of Products

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

6.4 BLINDING AND CODE-BREAKING PROCEDURES

This study will be conducted in a modified double-blind method, in which only designated staffs at each study site will know which vaccine has been administered to the subjects. The subjects, the subjects' parents / legally acceptable representatives and the Investigator in charge of the safety assessment will be blinded in order to decrease the potential bias in safety assessments.

Furthermore, the Sponsor and laboratory personnel performing the serology testing will also remain blinded to treatment assignments throughout the study until database lock.

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

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

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

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

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

6.5 RANDOMIZATION AND ALLOCATION PROCEDURES

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and sign the ICF (subjects 20 to 55 years of age) or sign the assent form (subjects 7 to 19 years of age) and whose parent / legally acceptable representative signs the ICF (subjects 2 to 19 years of age) will be randomly assigned to Group 1 or Group 2 in a 1:1 ratio, stratified according to age (children, adolescents and adults) such that each of Groups 1 and 2 will have approximately 180 subjects.

Study site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the vaccine dose number and have the study site staff confirm it. The full detailed procedures for group allocation are described in the IRT operation manuals. If the subject is not eligible to participate in the study, then the information will only be recorded on the screening/enrollment log.

Subject numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example, Subject 392000100005 is the fifth subject enrolled in Center Number 1 in Japan (392 being the Japan country code).

Subject numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT and an internal system.

6.6 TREATMENT COMPLIANCE

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

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

6.7 CONCOMITANT MEDICATION AND OTHER THERAPIES

At the time of enrollment, ongoing medications and other therapies (e.g., blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during 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 study (D30 [+14 days]).

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

- Category 1: antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immune modulators.
  Note: inhaled and topical steroids should not be captured.
- Category 2: Reportable medications used to define the Per-Protocol Analysis Set (PPAS). For example:
  - Influenza and other non-study vaccines: Influenza vaccine in the 2 weeks preceding the study vaccination up to the subject's termination from the study and any other vaccines (other than the study vaccine) in the 4 weeks preceding the study vaccination up to the subject's termination from the study
  - 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 study vaccination and the 4 weeks following the study vaccination
- Category 3: Oral or injectable antibiotics, which may interfere with bioassays used for antibody testing when taken before a blood draw.

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

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

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

- Trade name or generic 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 will not be recorded. Homeopathic medication will not be recorded. Topical treatment 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.

Restricted treatments during the study period

- Influenza and other non-study vaccines
- Immune globulins, blood or blood-derived products
- Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy, or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks)
- Oral or injectable antibiotics

7 MANAGEMENT OF SAMPLES

Blood samples for the assessment of antibody responses will be collected at Visit 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 Visit 1 and 2, 5 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the study site staff performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label, and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

7.2 SAMPLE PREPARATION

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

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours 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 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 consent of the subject or subject's parent / legally acceptable representative for future use of subject's samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

7.3 SAMPLE STORAGE AND SHIPMENT

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at −20°C or below. The temperature will be monitored and documented on the appropriate form during the entire study. If it rises above −10°C for any period of time, the Sponsor's monitoring staff must be notified. See the sample handling procedures for further details.

Sample collection by a logistics vendor will be made only after appropriate monitoring, and following notification of the Sponsor's monitoring staff. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the logistics vendor. Again, temperatures will be monitored. Shipments must be compliant with the United Nations Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to GCI at Sanofi Pasteur. The address is provided in the sample handling procedures.

7.4 FUTURE USE OF STORED BIOLOGICAL SAMPLES FOR RESEARCH

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 25 years after the end of the study. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

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

8 CLINICAL SUPPLIES

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

The means for performing EDC will be defined by the Sponsor. If a computer is provided by the Sponsor, 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 site staff must contact the Sponsor, indicating the quantity required. Contact information is provided in the clinical study protocol (See Names and Addresses).

9 ENDPOINTS AND ASSESSMENT METHODS

9.1 PRIMARY ENDPOINTS AND ASSESSMENT METHODS

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoint(s) for the evaluation of immunogenicity is:

Vaccine seroresponse (see Section 12.1.1.1) of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (Visit 1, D0, before vaccination) and at Visit 2 (D30 [+14 days]) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra® (Group 1 versus Group 2).

9.1.1.2 Immunogenicity Assessment Methods

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

Antibodies to meningococcal antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in a serum bactericidal assay utilizing human complement. 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 lower limit of quantitation (LLOQ) of the hSBA assay is a titer of 1:4.

This method will be performed on all blood samples (blood sampling [BL] 0001 and BL0002).

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

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 SECONDARY ENDPOINTS AND ASSESSMENT METHODS

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

The secondary endpoint for immunogenicity is:

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and after vaccination at D30 (+14 days) for all groups.

- hSBA vaccine seroresponse
- Proportion of subjects with hSBA titer ≥1:4 and ≥1:8
- hSBA GMT
- hSBA titer distribution and reverse cumulative distribution curve (RCDC)
- Proportion of subjects with hSBA titer ≥4-fold rise from baseline (Visit 1, D0, before vaccination) to after vaccination (Visit 2, D30 [+14 days])

9.2.1.2 Immunogenicity Assessment Methods

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

9.2.2 Safety

9.2.2.1 Safety Definitions

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

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[2]
- Requires inpatient hospitalization or prolongation of existing hospitalization[3]
- Results in persistent or significant disability/incapacity[4]
- 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.

[2] 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.

[3] 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.

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

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 the Sponsor:

Immediate Event/Reaction:

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

Solicited Reaction:

A solicited reaction is an “expected” adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (e.g., injection site pain or headache occurring between D0 and D7 post-vaccination).

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

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

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 D7 is a solicited reaction (i.e., prelisted in the protocol and CRB), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

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

Systemic AE:

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

9.2.2.2 Safety Endpoints

The secondary endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination, of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) injection site reactions occurring up to 7 days after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to Visit 2 after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the study from Visit 1 (D0) to Visit 2 (D30 [+14 days]) after vaccination.

9.2.2.3 Safety Assessment Methods

At Visit 2, the Investigator or a delegate will ask the subject or subject's parent / legally acceptable representative about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.2.2.3.1 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.

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

After vaccination, subjects or subjects' parents / legally acceptable representatives 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 or subjects' parents / legally acceptable representatives in the diary card on the day of vaccination and for the next 7 days (i.e., D0 through D7) until resolution:

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

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

- None
- Medication
- Health care provider contact
- Hospitalized

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

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

Table 1, Table 2 and Table 3 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 1 - Solicited injection site reactions for Children (2 to 9 years of age): terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration
Diary card term	Pain	Redness	Swelling	Hardening
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.	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.
Intensity scale[a]	Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm

a For the subjective reaction of pain, subjects or subjects' parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness, swelling and hardening, 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 2 - Solicited injection site reactions for Adolescents (10 to 17 years of age) or Adults (18 to 55 years of age): terminology, definitions, and intensity scales

CRB term (MedDRA LLT)	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration
Diary card term	Pain	Redness	Swelling	Hardening
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.	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.
Intensity scale[a]	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	Grade 1: ≥25 to ≤50 mm Grade 2: ≥51 to ≤100 mm Grade 3: >100 mm

a For the subjective reaction of pain, subjects or subjects' parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness, swelling and hardening, 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 3 - Solicited systemic reactions for Children, Adolescents or Adults (2 to 55 years of age): terminology, definitions, and intensity scales

CRB term (MedDRA LLT)	Fever	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[a]	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.

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

Important notes for the accurate assessment of temperature:

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

9.2.2.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, subjects or subjects' parents / legally acceptable representatives will be instructed to record any other medical events that may occur during the 30-day (+14-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 inclusion until 30 days (+14 days) after vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE. See Section 10 for further details on SAE reporting.

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

- Start and stop dates[5]
- 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 1, Table 2 and Table 3).

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

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

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

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

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

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.2.2.3.4.

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

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

- Whether the AE was serious

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

- Whether the AE caused study discontinuation

9.2.2.3.4 Assessment of Causality

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

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

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

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

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

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 OBSERVATIONAL ENDPOINTS AND ASSESSMENT METHODS

There are no observational objectives 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 within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the IP. It is the responsibility of the Investigator to request all necessary documentation (e.g., 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 REPORTING BY THE INVESTIGATOR

In the case of a SAE, the Investigator must immediately:

- ENTER (within 24 hours) all the information related to the SAE in the appropriate screens of the CRB; the system will automatically send the notification to the Sponsor after approval by the Investigator within the CRB or after a standard delay.
- All further data updates should be recorded in the CRB as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, subject status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, any effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.
- A back-up plan is used (using paper flow) when the CRB system does not work.

Back-up plan

- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) in the CRB to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical study protocol.
- All further documentation should be sent to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.

There may be instances when photocopies of medical records for certain cases are requested by the Sponsor. In this case, the Investigator should ensure that the subject's identity is protected and the subject's identifiers in the clinical study are properly mentioned on any photocopy of source document provided to the Sponsor.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the subject and considered by the Investigator to be caused by the IP with a reasonable possibility, should be reported to the monitoring team.

10.2 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 IP, other products (e.g., a benefit vaccine), or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.3 ASSESSMENT OF CAUSALITY

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.2.2.3.4.

Following this, the Global Safety Officer of Sanofi Pasteur 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).

10.4 REPORTING SAES TO HEALTH AUTHORITIES AND IRBS/IECS

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 Sponsor will be responsible for informing the IRBs or IECs 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 sites, will be given to study participants for the recording of daily safety information as described in Section 9.2.2.3. These diary cards will include prelisted terms and intensity scales (see Table 1, Table 2 and Table 3) as well as areas for free text to capture additional safety information or other relevant details. Subjects or subjects' parents / legally acceptable representatives will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects or subjects' parents / legally acceptable representatives on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the subjects or subjects' parents / legally acceptable representatives to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (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 study 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 leaves 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 Global Safety Officer of Sanofi Pasteur, and SMM of Sanofi Pasteur and Sanofi.K.K. 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 Sponsor CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and/or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical data will be submitted to the Investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

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

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

11.3 DATA REVIEW

A blind review of the data is anticipated through the data review process led by CDM 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 Primary Objective

12.1.1.1 Primary Objective

Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse.

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

Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$
Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$

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

*Vaccine seroresponse for serogroups A, C, Y, and W is defined as post-vaccination hSBA titers ≥1:16 for subjects with pre-vaccination hSBA titers <1:8 or at least a 4-fold increase in hSBA titers from pre- to post-vaccination for subjects with pre-vaccination hSBA titers ≥1:8.

For the 4 non-inferiority hypothesis using the seroresponse rates, the CI of the difference in proportions will be computed using the Wilson Score method without continuity correction (35). The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

12.1.2 Hypotheses and Statistical Methods for Secondary Objective

12.1.2.1 Secondary Objective

Immunogenicity

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in each lot of MenACYW conjugate vaccine and Menactra®.

In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages (36). For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed. RCDC figures will be provided for the antibody titers against meningococcal serogroups.

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

- hSBA vaccine seroresponse rate and 95% CI
- Proportion of subjects with hSBA titer ≥1:4 and ≥1:8 and 95% CI
- hSBA GMT and 95% CI
- hSBA titer distribution and RCDCs
- Proportion of subjects with hSBA titer ≥4-fold rise from baseline (Visit 1, D0, before vaccination) to after vaccination (Visit 2, D30 [+14 days]) and 95% CI

Safety

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

The frequency and percentage of subjects who had solicited injection site and systemic reactions and their 95% CIs will be provided. These events will be tabulated by type of reactions and intensity for each study group, as well as by other categories specified in the endpoints.

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

12.2 ANALYSIS SETS

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

12.2.1 Full Analysis Set

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

12.2.2 Safety Analysis Set

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

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

12.2.3 Per-Protocol Analysis Set

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

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

12.2.4 Populations Used in Analyses

The primary immunogenicity analyses will be performed on the PPAS, and will be confirmed on the FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

All safety analyses will be performed on the SafAS. Subjects will be analyzed according to the vaccine they actually received.

12.3 HANDLING OF MISSING DATA AND OUTLIERS

12.3.1 Safety

No replacement will be done. However, missing relationship will be considered as related at the time of statistical analysis. Details will be described in the SAP.

12.3.2 Immunogenicity

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

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

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

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

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

12.3.3 Efficacy

Not applicable.

12.4 INTERIM/PRELIMINARY ANALYSIS

No interim/preliminary analyses are planned.

12.5 DETERMINATION OF SAMPLE SIZE AND POWER CALCULATION

Approximately 360 healthy children, adolescents and adults (180 subjects per group) will be randomly assigned in a 1:1 ratio to the following vaccine groups:

- Group 1 (investigational): MenACYW conjugate vaccine (180 subjects)
- Group 2 (control): Menactra® (180 subjects)

[redacted]

Table 4 - Power of the study based on the primary objective of non-inferiority with [redacted] evaluable subjects per group

Serogroup	Estimated[a] MenACYW conjugate vaccine	Estimated[b] Menactra®	Non-inferiority margin	Power
[redacted]				

[redacted]

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/enrollment 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 Investigator or study coordinator will obtain verbal clarification from the subject or subject's parent / legally acceptable representative, enter the response into the "Investigator's comment" page of the diary card or source document, and transfer the information to the CRB.

The Investigator must print[6] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

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

13.3 CONFIDENTIALITY OF DATA, DATA PROTECTION, AND ACCESS TO SUBJECT RECORDS

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

[6] Unless the electronic medical records are determined to be appropriate at site selection, in which case they are acceptable on their own.

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation). Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

The race and ethnicity of each subject will be collected in this study because these data are required for submissions for licensure in countries which require an analysis of results by race and ethnicity.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

The subject or subject's parent / legally acceptable representative must be informed that subject's personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject or subject's parent / legally acceptable representative.

The subject or subject's parent / legally acceptable representative must be informed that subject's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4 MONITORING, AUDITING, AND ARCHIVING

13.4.1 Monitoring

Before the start of the study (i.e., before the inclusion of the first subject in the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's monitoring 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 Sponsor's monitoring staff 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 guidelines for detailed study procedures such as the product management, sample-handling procedures and IRT operation manuals.

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

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

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

13.4.2 Audits and Inspections

For the purpose of ensuring compliance with the clinical study protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified, and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

13.4.3 Archiving

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 25 years after the end of the clinical study unless local regulations or institutional policies require a longer retention period.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical study completion or discontinuation. No records may be destroyed during the retention period without the written approval of the Sponsor.

No records may be transferred to another location or party without written notification to the Sponsor.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

13.4.4 Responsibilities of Investigator(s)

The Investigator is required to ensure compliance with all procedures required by the clinical study protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical study protocol (with the help of the CRF, discrepancy resolution form, or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to the Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the subject’s data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical study in accordance with the clinical study protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical study protocol and all necessary information.

13.4.5 Responsibilities of the Sponsor

The Sponsor of this clinical study is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical study as regards ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical study.

At regular intervals during the clinical study, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and subject compliance with clinical study protocol requirements, and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: subject and/or subject's parent / legally acceptable representative informed consent (and assent), subject recruitment and follow-up, SAE documentation and reporting, AE documentation, IP allocation, IP accountability, concomitant therapy use, and quality of data.

13.5 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical study, including, but not limited to, the clinical study protocol, personal data in relation to the subjects, the CRFs, the IB, and the results obtained during the course of the clinical study, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical study protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical study.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical study, to the exclusion of any use for their own or for a third party's account.

13.6 PROPERTY RIGHTS

All information, documents and IP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated study site staff / Sub-investigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical study in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical study.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

13.7 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical studies under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC or regulatory authorities in countries requiring this document.

13.8 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.

13.9 PUBLICATION POLICY

Data derived from this study are the exclusive property of the Sponsor and Sanofi Pasteur. Any publication or presentation related to the study must be submitted to the Sponsor and 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, the Sponsor and Sanofi Pasteur shall be offered an association with all such publications, it being understood that the Sponsor and Sanofi Pasteur is entitled to refuse the association.

The Sponsor and 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 the Sponsor and 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.

The Sponsor's and Sanofi Pasteur's reviews can be expedited to meet publication guidelines.

14 REFERENCES LIST

1. Granoff DM, Pelton S, Harrison LH. Meningococcal vaccines. Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 6th ed. Philadelphia (PA): Saunders (Elsevier). 2013:388-418.

2. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine. 2009 Jun 24;27 Suppl 2:B51-63.

3. Harrison OB, Claus H, Jiang Y, Bennett JS, Bratcher HB, Jolley KA, et al. Description and nomenclature of Neisseria meningitidis capsule locus. Emerg Infect Dis. 2013 Apr;19(4):566-73.

4. Pollard AJ. Global epidemiology of meningococcal disease and vaccine efficacy. Pediatr Infect Dis J. 2004 Dec;23(12 Supp):S274-9.

5. Kvalsvig AJ, Unsworth DJ. The immunopathogenesis of meningococcal disease. J Clin Pathol. 2003 Jun;56(6):417-22.

6. Sidikou F, Djibo S, Taha MK, Alonso JM, Djibo A, Kairo KK, et al. Polymerase chain reaction assay and bacterial meningitis surveillance in remote areas, Niger. Emerg Infect Dis. 2003 Nov;9(11):1486-8.

7. World Health Organization. Meningococcal disease, serogroup W135 (update). WER. 2001;76(28):213-4.

8. Ibarz-Pavón AB, Gabastou J-M. Improving surveillance and characterization of meningococcal disease in Latin America and the Caribbean region: a collaborative research program for strengthening regional surveillance network based on laboratory evidence of N. meningitidis. Final Report 2010-2013. Available online: https://partners.sanofi.com/global/menactra/Documents/PAHO%20SIREVA%202%20Meningococcal%20Surveillance%20Final%20Report.pdf. Accessed 15 October 2019.

9. Ceyhan M, Yildirim I, Balmer P, Borrow R, Dikici B, Turgut M, et al. A prospective study of etiology of childhood acute bacterial meningitis, Turkey. Emerg Infect Dis. 2008 Jul;14(7):1089-96.

10. Kilic A, Urwin R, Li H, Saracli MA, Stratton CW, Tang YW. Clonal spread of serogroup W135 meningococcal disease in Turkey. J Clin Microbiol. 2006 Jan;44(1):222-4.

11. Liang J, Peng GW, Zhou H. Epidemiological analysis on serogroup W135 Neisseria meningitidis firstly isolated from patient in Guangdong province. Zhonghua Liu Xing Bing Xue Za Zhi. 2008 Sep;29(9):948.

12. Efron AM, Sorhouet C, Salcedo C, Abad R, Regueira M, Vázquez JA. W135 invasive meningococcal strains spreading in South America: significant increase in Argentina. J Clin Microbiol. 2009 Jun;47(6):1979-80.

13. Weidlich L, Baethgen LF, Mayer LW, Moraes C, Klein CC, Nunes LS, et al. High prevalence of Neisseria meningitidis hypervirulent lineages and emergence of W135:P1.5,2:ST-11 clone in Southern Brazil. J Infect. 2008 Oct;57(4):324-31.

14. Barroso DE, Rebelo MC. Recognition of the epidemiological significance of Neisseria meningitidis capsular serogroup W135 in the Rio de Janeiro region, Brazil. Mem Inst Oswaldo Cruz. 2007 Sep;102(6):773-5.

15. Boisier P, Nicolas P, Djibo S, Taha MK, Jeanne I, Maïnassara HB, et al. Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in Niger. Clin Infect Dis. 2007 Mar 1;44(5):657-63.

16. Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Cartter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999 Dec;180(6):1894-901.

17. Canadian Immunization Committee and Public Health Agency of Canada. Advice for consideration of quadrivalent (A, C, Y, W135) meningococcal conjugate vaccine, for use by provinces and territories. CCDR. 2010;36(S2):1-35.

18. Bröker M, Jacobsson S, Kuusi M, Pace D, Simões MJ, Skoczynska A, et al. Meningococcal serogroup Y emergence in Europe: update 2011. Hum Vaccin Immunother. 2012 Dec 1;8(12):1907-11.

19. Cohn AC, MacNeil JR, Harrison LH, Hatcher C, Theodore J, Schmidt M, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease. Clin Infect Dis. 2010 Jan 15;50(2):184-91.

20. National Foundation for Infectious Diseases. Addressing the challenges of Serogroup B meningococcal disease outbreaks on campuses: A report by the National Foundation for Infectious Diseases. May 2014. Available online: https://www.nfid.org/wp-content/uploads/2019/08/meningococcal-b-report.pdf. Accessed 15 October 2019.

21. Centers for Disease Control and Prevention. Interim guidance for control of serogroup B meningococcal disease outbreaks in organizational settings. Available online: http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf. Accessed 23 February 2015.

22. European Centre for Disease Prevention and Control. Annual epidemiological report 2014 - Vaccine-preventable diseases - invasive bacterial diseases. Stockholm: ECDC; 2015. Available online: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/AER-VPD-IBD-2014.pdf. Accessed 15 October 2019.

23. Public Health England. Increase in endemic Meningococcal group W (MenW) ST-11 complex associated with severe invasive disease in England and Wales. Health Protection Weekly Report. Vol 8 No 41 Published on: 24 October 2014. Available online:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/367588/hpr4114.pdf). Accessed 15 October 2019.

24. Törös B, Thulin Hedberg S, Jacobsson S, Fredlund H, Olcén P, Mölling P. Surveillance of invasive Neisseria meningitidis with a serogroup Y update, Sweden 2010 to 2012. Euro Surveill. 2014 Oct 23;19(42).

25. Hedberg ST, Törös B, Fredlund H, Olcén P, Mölling P. Genetic characterisation of the emerging invasive Neisseria meningitidis serogroup Y in Sweden, 2000 to 2010. Euro Surveill. 2011 Jun 9;16(23).

26. The European Meningococcal Disease Society. 11th EMGM Meeting, 18-20 May 2011. Ljubljana Slovenia. Poster abstracts P035, 037-040. Available online: http://emgm.eu/meetings/emgm2011/abstracts.pdf. Accessed 15 October 2019.

27. Centers for Disease Control and Prevention. Active Bacterial Core surveillance (ABCs) Report: Neisseria meningitidis, 2013. Available online: https://www.cdc.gov/abcs/reports-findings/survreports/mening13.html. Accessed 15 October 2019.

28. National institute of infectioous diseases. Invasive meningococcal infection, April 2013-October 2017, Japan. Infectious Agents Surveillance Report (IASR). 2018 Jan;39(1). Available online: https://www.niid.go.jp/niid/en/basic-science/865-iasr/7802-455te.html. Accessed 15 October 2019.

29. Centers for Disease Control and Prevention. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine--United States, June 2005-September 2006. MMWR Morb Mortal Wkly Rep. 2006 Oct 20;55(41):1120-4.

30. Velentgas P, Amato AA, Bohn RL, Chan KA, Cochrane T, Funch DP, et al. Risk of Guillain-Barré syndrome after meningococcal conjugate vaccination. Pharmacoepidemiol Drug Saf. 2012 Dec;21(12):1350-8.

31. Committee to Review Adverse Effects of Vaccines; Institute of Medicine; Stratton K, Ford A, Rusch E, Clayton EW, editors. Diphtheria toxoid, tetanus toxoid, and acellular pertussis containing vaccines. Adverse effects of vaccines:evidence and causality. Washington (DC): National Academies Press (US). 2012:557-8.

32. Institute of Medicine (US) Vaccine Safety Committee; Stratton KR, Howe CJ, Johnston RB Jr., editors. Adverse events associated with childhood vaccines; evidence bearing on causality. Washington (DC): National Academy Press (US). 1994:67-117.

33. Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and mortality weekly report (MMWR). 2011;60(2):1-60.

34. Sanofi K.K. Menactra® intramuscular injection [package insert].

35. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998 Apr;17(8):873-90.

36. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998 Apr;17(8):857-72.

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