

NCT Number: NCT02842853

Immune Lot Consistency, Immunogenicity, and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults Aged 10 to 55 Years

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 United States.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET43
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid Solution / Intramuscular
Indication For This Study:	MenACYW conjugate vaccine as a single dose in adolescents and adults aged 10 to 55 years
Version and Date of the SAP core body part:	Version 2.0, 1 FEBRUARY, 2018

Table of Contents

List of Tables	6
List of Abbreviations	7
1 Introduction	8
2 Trial Objectives	9
2.1 Primary Objectives.....	9
2.2 Secondary Objectives.....	9
2.3 Observational Objectives.....	9
3 Description of the Overall Trial Design and Plan	10
3.1 Trial Design	10
3.2 Trial Plan.....	10
4 Endpoints and Assessment Methods	13
4.1 Primary Endpoints and Assessment Methods.....	13
4.1.1 Immunogenicity.....	13
4.1.1.1 Immunogenicity Endpoints	13
4.1.1.2 Immunogenicity Assessment Method	13
4.1.2 Safety.....	13
4.1.3 Efficacy.....	13
4.2 Secondary Endpoints and Assessment Methods.....	14
4.2.1 Immunogenicity.....	14
4.2.1.1 Immunogenicity Endpoints	14
4.2.1.2 Immunogenicity Assessment Method	14
4.2.2 Safety	14
4.2.3 Efficacy.....	14
4.3 Observational Endpoints and Assessment Methods	15
4.3.1 Immunogenicity.....	15
4.3.1.1 Immunogenicity Endpoints	15
4.3.1.2 Immunogenicity Assessment Methods	15
4.3.2 Safety	15
4.3.2.1 Safety Definitions.....	15
4.3.2.2 Safety Endpoints	18
4.3.2.3 Safety Assessment Method	19

4.3.2.3.1	Immediate Post-vaccination Surveillance Period	19
4.3.2.3.2	Reactogenicity (Solicited Reactions From Day 0 to Day 07 After Vaccination).....	19
4.3.2.3.3	Unsolicited Non-serious Adverse Events From Day 0 to Day 30 After Vaccination	23
4.3.2.3.4	Serious Adverse Events	24
4.3.2.3.6	Medically-Attended Adverse Events	24
4.3.2.3.7	Assessment of Causality	24
4.4	Derived Endpoints: Calculation Methods	25
4.4.1	Safety	25
4.4.1.1	Solicited Reactions.....	25
4.4.1.1.1	Daily Intensity.....	25
4.4.1.1.2	Maximum Overall Intensity.....	25
4.4.1.1.3	Presence	26
4.4.1.1.4	Time of Onset	26
4.4.1.1.5	Number of Days of Occurrence	26
4.4.1.1.6	Overall Number of Days of Occurrence	26
4.4.1.1.7	Ongoing	26
4.4.1.2	Unsolicited Non-serious AEs.....	27
4.4.1.2.1	Presence	27
4.4.1.2.2	Intensity	27
4.4.1.2.3	Last Vaccination	27
4.4.1.2.4	Time of Onset	27
4.4.1.2.5	Duration	27
4.4.1.3	SAEs.....	28
4.4.1.3.1	Last Vaccination	28
4.4.1.3.2	Time of Onset	28
4.4.1.3.3	Duration	28
4.4.1.4	Medically-Attended Adverse Event (MAAE)	28
4.4.1.5	Other Safety Endpoints	28
4.4.1.5.1	Pregnancy.....	28
4.4.1.5.2	Action Taken.....	29
4.4.1.5.3	Seriousness.....	29
4.4.1.5.4	Outcome.....	29
4.4.1.5.5	Causality	29
4.4.1.5.6	AEs Leading to Study Discontinuation	29
4.4.2	Immunogenicity.....	29
4.4.2.1	Computed Values for Analysis	29
4.4.2.2	Seroprotection	30

4.4.2.3	Fold-rise	30
4.4.2.4	Vaccine Seroresponse	30
4.4.3	Efficacy.....	30
4.4.4	Derived Other Variables.....	31
4.4.4.1	Age for Demographics	31
4.4.4.2	Subject Duration.....	31
4.4.4.3	Duration of the Study	31
4.4.4.4	MAAEs from Visit 1 to Visit 2	31
5	Statistical Methods and Determination of Sample Size.....	31
5.1	Statistical Methods.....	32
5.1.1	Hypotheses and Statistical Methods for Primary Objectives	32
5.1.1.1	Primary Objective 1	32
5.1.1.1.1	Hypotheses.....	32
5.1.1.1.2	Statistical Methods.....	33
5.1.1.2	Primary Objective 2	33
5.1.1.2.1	Hypothesis	33
5.1.1.2.2	Statistical Methods.....	34
5.1.2	Hypotheses and Statistical Methods for Secondary Objectives	35
5.1.2.1	Secondary Objective 1	35
5.1.2.1.1	Hypotheses.....	35
5.1.2.1.2	Statistical Methods.....	35
5.1.2.2	Secondary Objective 2	35
5.1.2.2.1	Hypotheses.....	35
5.1.2.2.2	Statistical Methods.....	36
5.1.2.3	Secondary Objective 3	36
5.1.2.3.1	Hypotheses.....	36
5.1.2.3.2	Statistical Methods.....	36
5.1.2.4	Secondary Objective 4	36
5.1.2.4.1	Hypothesis	36
5.1.2.4.2	Statistical Methods.....	36
5.1.3	Statistical Methods for Observational Objectives	37
5.1.3.1	Hypothesis.....	37
5.1.3.2	Statistical Methods	37
5.1.3.2.1	Immunogenicity	37
5.1.3.2.2	Safety	38
5.1.4	Complementary Output	39
5.2	Analysis Sets.....	40
5.2.1	Full Analysis Set.....	40
5.2.2	Safety Analysis Set.....	40
5.2.3	Per-Protocol Analysis Set.....	40

5.2.4	Other Analysis Set.....	41
5.2.5	Populations Used in Analyses	41
5.3	Handling of Missing Data and Outliers	41
5.3.1	Safety.....	41
5.3.1.1	Immediate.....	41
5.3.1.2	Causality.....	42
5.3.1.3	Measurements	42
5.3.1.4	Intensity.....	42
5.3.1.5	Start Date and Stop Date	42
5.3.2	Immunogenicity.....	42
5.3.3	Efficacy.....	42
5.4	Interim / Preliminary Analysis.....	42
5.5	Determination of Sample Size and Power Calculation.....	43
5.5.1	Calculation of Sample Size	43
5.5.2	Power Calculation for the Primary Objectives	43
5.6	Data Review for Statistical Purposes.....	44
5.7	Changes in the Conduct of the Trial or Planned Analyses	44
6	References List.....	45

List of Tables

Table 3.1: Table of study procedures	11
Table 4.1: Solicited injection site reactions: terminology, definitions, and intensity scales.....	21
Table 4.2: Solicited systemic reactions: terminology, definitions, and intensity scales	22
Table 5.1: Descriptive statistics produced.....	32
Table 5.2: Statistical analyses for safety observational objective	38
Table 5.3: Power of the study based on Primary Objective 1 of equivalence.....	43
Table 5.4: Power of the study based on Primary Objective 2 of non-inferiority	43

List of Abbreviations

AE	adverse event
AR	adverse reaction
BL	blood sample
CFU	colony-forming unit
CI	confidence interval
CRF	electronic case report form
CSR	clinical study report
D	day
EDC	electronic data capture
FAS	full analysis set
GM	geometric mean
GMTRs	Geometric mean titer ratios
GMTs	geometric mean titers
hSBA	serum bactericidal assay using human complement
ICH	International Conference on Harmonisation
IMD	invasive meningococcal disease
LLOQ	lower limit of quantitation
LLT	lowest level term
MA	memory aid
MAAEs	medically-attended adverse events
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
NM	non-measurable
NR	not reportable
PPAS	Per-Protocol Analysis Set
PT	preferred term
RCDC	reverse cumulative distribution curve
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	statistical analysis plan
SOC	system organ class (primary)
TLF	table(s), listing(s), and figure(s)
UAR	unexpected adverse reaction
ULOQ	upper limit of quantitation
V	Visit

1 Introduction

This trial will evaluate the immune lot consistency of Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine), evaluate the immune non-inferiority versus Menactra[®], and describe the safety and additional immunogenicity of study vaccines in adolescents and adults 10 to 55 years of age.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis* (*N. meningitidis*), a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (2) (3) (4).

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 (5). In the US, the incidence rate of IMD was 0.14 per 100,000 in all ages; 0.83 per 100,000 in infants less than 1 year; 0.62 per 100,000 in toddlers 1 year of age; 0.27 per 100,000 in children 2 to 4 years of age; and 0.02 per 100,000 in children 5 to 17 years of age in 2013. The age specific incidence rate per 100,000 was 0.08 in adults 50 to 64 years of age, 0.03 in adults 65 to 74 years of age, 0.14 in adults 75 to 84 years of age, and 0.43 in adults 85 years of age and older in 2013 (6).

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.

MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. The formulation has been evaluated in over 650 subjects (infants, toddlers, and adults > 55 years of age) in MET39 and MET44. Both the studies showed the potential of the candidate vaccine as a potent immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials. Additionally, the vaccine has been evaluated in another Phase II study in subjects aged 10 to 17 years in the US (MET50). The immunological analysis is still ongoing, however, no new safety concerns or signals have been identified to date.

The purpose of MET43 is to demonstrate the immune lot consistency of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine. Additionally, MET43 has the purpose of demonstrating 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 to those observed following the administration of a single dose of Menactra[®]. Generation of immune lot consistency data and immune non-inferiority versus a licensed vaccine is an important regulatory requirement for registration of this vaccine.

2 Trial Objectives

2.1 Primary Objectives

- 1) To demonstrate the immune lot consistency of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine with respect to serum bactericidal assay using human complement (hSBA) geometric mean titers (GMTs)
- 2) 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 (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra[®]

2.2 Secondary Objectives

- 1) 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 (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra[®] in the adult population (18 to 55 years old)
- 2) 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 (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra[®] in the adolescent population (10 to 17 years old)
- 3) To compare the hSBA seroresponses of meningococcal serogroups A, C, Y, and W for each of 3 lots of MenACYW conjugate vaccine 30 days (+14 days) after vaccination
- 4) To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine to those observed following the administration of Menactra[®]

2.3 Observational 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 the licensed Menactra[®]

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is 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 United States.

Healthy, meningococcal-vaccine naïve adolescents and adults will be 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

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

Solicited adverse event (AE) information will be collected for 7 days after vaccination, unsolicited AE information will be collected from Visit 1 (Day [D] 0) to Visit 2 (D30 [+14 days]), and serious adverse event (SAE) information will be collected from D0 through D180 (+14 days) after vaccination.

Medically-attended adverse events (MAAEs) information will be collected throughout the study from Visit 1 to Visit 2 (as part of the collection of unsolicited AE information) and from Visit 2 through D180 (+14 days) (as MAAEs).

3.2 Trial Plan

A schedule of assessments and study vaccinations is provided in the Table of Study Procedures (see Table 3.1).

Table 3.1: Table of study procedures

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

Visit/Contact	Visit 1	Telephone Call 1	Visit 2	Telephone Call 2
Trial timelines (days)	Day 0	Day 8	Day 30	Day 180
Time windows (days)	--	+2 days	+14 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*	X			
Review of temporary contraindications for blood sampling†			X	
Randomization/allocation of subject number	X			
Blood sampling (BL), 10 mL‡	BL1		BL2	
Vaccination§	X			
Immediate surveillance (30 minutes)	X			
Diary card provided	X			
Telephone call		X**		X††
Recording of solicited injection site & systemic reactions	D0 to D07			
Recording of unsolicited AEs	Visit 1 to Visit 2			
Diary card reviewed and collected			X	
Recording of MAAEs‡‡				After Visit 2 to TC2
Reporting of SAEs	To be reported throughout the study period			
Collection of reportable concomitant medications	X		X	
Memory aid (MA) provided§§			X	
Termination of active phase of trial			X	
Completion of 6-month follow-up				X

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

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

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

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

**This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported, and will remind the subject / subject's parent / guardian 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.

††Staff will contact the subject / subject's parent / guardian by telephone at 6 months (180 days +14 days) after vaccination at Visit 1 to identify the occurrence of any MAAEs as well as SAEs not yet reported.

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

§§The MA is used for the recording of SAEs and MAAEs. The site staff will make a telephone call to the subject/subject's parent / guardian to obtain the information 180 days (+14 days) after the vaccination at Visit 1. Since the timeframe between Visit 1 and Visit 2 (inclusive) will be captured in the diary card, the MA will be used to collect SAE and MAAE data from Visit 2 to TC2.

Vaccination

All subjects will receive a single dose of MenACYW conjugate vaccine (from 1 of the 3 lots [Lot 1, Lot 2, or Lot 3]) or Menactra[®] on D0.

Blood sampling

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

A, C, Y, and W antigens of MenACYW conjugate vaccine (Groups 1, 2, and 3) and Menactra[®] (Group 4) will be measured by hSBA for all subjects, and by serum bactericidal assay using baby rabbit complement (rSBA) for a subset of 100 subjects per treatment group.

Collection of safety data

- All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the electronic case report form (CRF).
- The subject or the subject's parent / guardian will record information in a diary card about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to Visit 2. SAEs will be reported throughout the duration of the trial.
- The subject or the subject's parent / guardian will record information about any possible SAEs and MAAEs in a memory aid (MA) from Visit 2 until the 6 month (+14 days) telephone call.
- In addition, the subject or subject's parent / guardian will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- Staff will contact the subject or the subject's parent / guardian by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card up to Visit 2 and to bring it back at Visit 2.
- The completed diary card will be reviewed with the subject and/or the subject's parent / guardian at Visit 2.
- Staff will contact the subject or the subject's parent / guardian by telephone at 6 months (+14 days) after vaccination to review the MA and identify the occurrence of any MAAEs, as well as SAEs that may have not been reported.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Immunogenicity

4.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

- 1) Geometric mean titer ratios (GMTRs) of antibodies against meningococcal serogroups A, C, Y, and W measured by hSBA 30 days (+14 days) after vaccination between lots for immune lot consistency
- 2) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra[®] (Groups 1 - 3 pooled versus Group 4)

4.1.1.2 Immunogenicity Assessment Method

[REDACTED]

4.1.2 Safety

There are no primary objectives for safety.

4.1.3 Efficacy

No clinical efficacy data will be obtained in the trial.

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Immunogenicity

4.2.1.1 Immunogenicity Endpoints

The secondary endpoints for immunogenicity are:

- 1) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra[®] adult study participants (Groups 1b, 2b, and 3b pooled versus Group 4b)
- 2) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra[®] adolescent study participants (Group 1a, 2a, and 3a pooled versus Group 4a)
- 3) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA 30 days (+14 days) following the administration of MenACYW conjugate vaccine (Groups 1, 2, and 3)
- 4) GMTRs of antibodies against meningococcal serogroups A, C, Y, and W measured by hSBA for the groups that received MenACYW conjugate vaccine (Groups 1 - 3 pooled) and Menactra[®] (Group 4)

4.2.1.2 Immunogenicity Assessment Method

The immunogenicity hSBA assessment method for the secondary endpoints is the same as that presented in Section 4.1.1.2.

4.2.2 Safety

There are no secondary objectives for safety.

4.2.3 Efficacy

No clinical efficacy data will be obtained in the trial.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Immunogenicity

4.3.1.1 Immunogenicity Endpoints

The observational endpoints for immunogenicity are:

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA and rSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination in a subset of subjects for all groups.

4.3.1.2 Immunogenicity Assessment Methods

[REDACTED]

4.3.2 Safety

4.3.2.1 Safety Definitions

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

^a T60: Time of incubation duration of 60 minutes

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening^a
- Requires inpatient hospitalization or prolongation of existing hospitalization^b
- Results in persistent or significant disability / incapacity^c

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

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

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

- Is a congenital anomaly / birth defect
- Is an important medical event^a

Adverse Reaction:

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

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

Unexpected Adverse Reaction (UAR):

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

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

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

- Symptom and
- Onset post-vaccination

Examples of solicited reactions include injection site pain between D0 and D07 post-vaccination or headache between D0 and D07.

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

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and / or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D07 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D07 is a solicited reaction, whereas headache starting on D08 post-vaccination is an unsolicited AE.

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

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

Injection Site Reaction:

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

Systemic AE:

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

Medically-Attended Adverse Event (MAAE)

An MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject or subject's parent/guardian to seek unplanned medical advice at a physician's office or Emergency Department. This definition excludes pre-planned medical office visits for routine pediatric check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. Physician contact made over the phone or by email will be considered a physician office visit for the purpose of MAAE collection. The outcome of the physician contact (whether it results in a prescription or not) will not be considered as a basis for reporting the event as an MAAE and all contacts should be reported. Sufficient data should be collected for the event to allow an assessment of the causality and diagnosis, if possible.

4.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

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

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

- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the trial.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness, relationship to vaccination, and outcome for MAAEs from Visit 2 to the 6-month follow-up contact. MAAEs will be collected as unsolicited AEs up to Visit 2.

4.3.2.3 Safety Assessment Method

At Visit 2, the Investigator or a delegate will ask the subject or parent / guardian 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 CRF according to the instructions provided by the Sponsor.

4.3.2.3.1 Immediate Post-vaccination Surveillance Period

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

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

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

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

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

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

- 0: None
- 1: Medication (self-medication with an existing prescription or over-the-counter medication)
- 2: Health care provider contact (no new medication prescribed)
- 3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)
- 4: Hospitalization (inpatient)

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

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

Table 4.1 and Table 4.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRF, together with the intensity scales.

Table 4.1: Solicited injection site reactions: terminology, definitions, and intensity scales

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

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

Table 4.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to $\geq 100.4^{\circ}\text{F}$ ($\geq 38.0^{\circ}\text{C}$)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: $\geq 100.4^{\circ}\text{F}$ to $\leq 101.1^{\circ}\text{F}$, or $\geq 38.0^{\circ}\text{C}$ to $\leq 38.4^{\circ}\text{C}$ Grade 2: $\geq 101.2^{\circ}\text{F}$ to $\leq 102.0^{\circ}\text{F}$, or $\geq 38.5^{\circ}\text{C}$ to $\leq 38.9^{\circ}\text{C}$ Grade 3: $\geq 102.1^{\circ}\text{F}$ or $\geq 39.0^{\circ}\text{C}$	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

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

Important Notes for the Accurate Assessment of Temperature:

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

4.3.2.3.3 Unsolicited Non-serious Adverse Events From Day 0 to Day 30 After Vaccination

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

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

- Start and stop dates^a
- Intensity of the event:
 - For measurable unsolicited non-serious AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 4.1 and Table 4.2)
 - Other unsolicited non-serious AEs will be classified according to the following intensity scale:
 - Grade 1: No interference with activity
 - Grade 2: Some interference with activity
 - Grade 3: Significant; prevents daily activity
- Action taken for each AE, if any (e.g., medication)

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

- 0: None
- 1: Medication (self-medication with an existing prescription or over-the-counter medication)
- 2: Health care provider contact (no new medication prescribed)
- 3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

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

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

4.3.2.3.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from inclusion until 180 days (+14 days) after vaccination.

Any SAE occurring at any time during the trial will be reported by the Investigator through the electronic data capture (EDC) system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE is to be reported, either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). The Investigator will assess the causal relationship between the SAE and the investigational product as either “Not related” or “Related”, as described in Section 4.3.2.3.7.

See protocol for further details on SAE reporting.

4.3.2.3.5 [REDACTED]

Not applicable.

4.3.2.3.6 Medically-Attended Adverse Events

MAAE information will be collected throughout the study. MAAEs that occur from Visit 1 (D0) to Visit 2 (D30[+14days]) will be recorded as unsolicited AEs on the diary card where the action taken category is 2 or 3 as part of all unsolicited AEs collected for this post-vaccination period. MAAEs that occur from Visit 2 (D30 [+14 days]) to D180 (+14 days) will be recorded as such in the MA. An MAAE that occurs within the study period but meets the definition of an SAE should be reported only on the SAE Reporting Form, but not on the MAAE page of the CRF. The Investigator will assess the causal relationship between the MAAE and the investigational or study product as either “Not related” or “Related”, as described in Section 4.3.2.3.7.

4.3.2.3.7 Assessment of Causality

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

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

^a ICH Guidelines, Clinical Safety Data Management E2A

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

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

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

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

For the derivation of daily intensities the following sequential steps will be applied:

- 1) Solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as “No” and with all daily records missing then all daily intensities will be derived as None.
- 2) For a temperature partially missing after decimal point, the data will be analyzed replacing “MD” (missing data) by zero. For example, a “39.MD” daily temperature will be considered as "39.0°C" at the time of analysis.
- 3) For non-measurable (NM) solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (NM) is Grade 3. Note the intensity could be considered “None” (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.4.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing: Missing presence

Subjects with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

4.4.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

- (stop date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the stop date is missing or incomplete (contains MD), the overall number of days of occurrence will be considered as Missing.

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

4.4.1.2 Unsolicited Non-serious AEs

4.4.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event. Grade 0 events should be included in the listing “Unsolicited non-serious adverse events not included in the safety analysis.”

4.4.1.2.2 Intensity

Intensity for unsolicited non-serious AE will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited non-serious AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule than the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.4.1.2.3 Last Vaccination

Last vaccination before any unsolicited non-serious AE is the study vaccination at Visit (V) 01.

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

- start date of the unsolicited non-serious AEs – date of previous vaccination

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited non-serious AEs will be analyzed “Within 30 days”, which corresponds to AEs with a time of onset between 0 and 30 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: Unsolicited non-serious AEs that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis, but will be listed separately.

4.4.1.2.5 Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

- stop date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if one or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

4.4.1.3 SAEs

4.4.1.3.1 Last Vaccination

The last vaccination before any SAE is defined as the study vaccination at V01.

4.4.1.3.2 Time of Onset

Time of onset will be computed using the same methodology than for unsolicited non-serious AEs described in Section 4.4.1.2.4.

SAEs will be analyzed throughout the study using the following periods:

- During the study (i.e., all SAEs occurred during the study)
- Within 30 days after vaccination

An SAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: SAEs that occurred before vaccination (negative time of onset) will not be included in analysis, but will be listed separately.

4.4.1.3.3 Duration

Duration will be computed using the same methodology than for unsolicited non-serious AEs described in Section 4.4.1.2.5.

4.4.1.4 Medically-Attended Adverse Event (MAAE)

MAAEs will be collected as unsolicited AEs in the diary card as part of all unsolicited AEs from D0 to the D30 (+14 days). Unsolicited AEs that have action taken categories 2 or 3 will be summarized and presented as MAAEs between D0 and D30. MAAEs that occur from D30 to D180 (+14 days) will be recorded as such in the MA. Calculation methods are the same as unsolicited non-serious AEs as described in Section 4.4.1.2.

4.4.1.5 Other Safety Endpoints

4.4.1.5.1 Pregnancy

This information will be listed as collected. No derivation or imputation will be done.

4.4.1.5.2 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.4.1.5.3 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.5.4 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.5.5 Causality

This information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.5.6 AEs Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination “Serious Adverse Event” or “Other adverse event” is checked.
- Safety overview table: A subject who has either the reason for early termination “Serious Adverse Event” or “Other adverse event” checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has “Reaction Leading to Termination” or “Event Leading to Termination” or “Serious Adverse Event Leading to Termination” checked on the termination form, that is at least Grade 1 and is within the time period indicated.
- System Organ Class/Preferred Term (SOC/PT) table: An event (solicited, unsolicited, or SAE) that has “Reaction Leading to Termination” or “Event Leading to Termination” or “Serious Adverse Event Leading to Termination” checked that is at least Grade 1 and is within the time period indicated.

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

In order to appropriately manage extreme values ($< \text{LLOQ}$ and $\geq \text{ULOQ}$) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each BL drawn:

- If a value is $< \text{LLOQ}$, then use the computed value $\text{LLOQ}/2$
- If a value is between $\geq \text{LLOQ}$ and $< \text{ULOQ}$, then use the value

- If a value is \geq ULOQ, then use the computed value ULOQ

4.4.2.2 Seroprotection

Not applicable

4.4.2.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows. Generally, for extreme values, this algorithm minimizes the numerator and maximizes the denominator.

- If the baseline computed value is $<$ LLOQ and the post-baseline computed value is $<$ LLOQ, then the fold-rise is 1
- If the baseline computed value is \geq LLOQ and the post-baseline computed value is \geq LLOQ, then the fold-rise is post-baseline computed value / baseline computed value
- If the baseline computed value is \geq 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 \geq LLOQ, then the fold-rise is post-baseline computed value /LLOQ

If the computed value is ≥ 4 , then the derived ≥ 4 -fold rises indicator will be "Yes" for that test, otherwise ≥ 4 -fold rises will be "No".

Note: If baseline or post-baseline is missing, then fold-rise is missing.

4.4.2.4 Vaccine Seroresponse

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

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

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

- A post-vaccination titer \geq 1:32 for subjects with pre-vaccination rSBA titer $<$ 1:8.
- A post-vaccination titer \geq 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer \geq 1:8

4.4.3 Efficacy

Not applicable

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

Age in years: (Date of vaccination - Date of birth +1) / 365.25

4.4.4.2 Subject Duration

The duration of a subject in the study is computed as follows: Maximum (date of last visit, date of term form) – (date of Visit 1) +1.

The duration of a subject in the study including follow-up is computed as follows: Maximum (date of last visit, date of term form, last date of follow-up contact) – (date of Visit 1) +1.

4.4.4.3 Duration of the Study

The duration of the study (until last visit) is computed as follows: Maximum of all subjects (date of last visit, date of termination form) – minimum for all subjects (date of Visit 1) +1.

The duration of the study (including follow-up) is computed as follows: Maximum of all subjects (date of last visit, date of termination form, date of last follow-up contact) – minimum for all subjects (date of Visit 1) +1

4.4.4.4 MAAEs from Visit 1 to Visit 2

MAAEs that occur from Visit 1 to Visit 2 will be recorded as unsolicited AEs on the diary card as part of all unsolicited AEs collected for this post-vaccination period. The unsolicited AEs that have action taken categories 2 (health care provider contact) or 3 (Health care contact + Medication) will be summarized and presented as MAAEs which occurred from Visit 1 to Visit 2.

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software or later.

The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics in Table 5.1 will be presented. The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (7)). For immunogenicity results, assuming that Log₁₀ transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log₁₀ (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	Categorical data	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	Categorical data	Solicited: Number and percentage (95% CIs) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	Categorical data (seroresponse, cutoff)	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / data)	Log ₁₀ : Mean and standard deviation. Anti-Log ₁₀ (work on Log ₁₀ distribution, and anti-Log ₁₀ applied): GM, 95% CI of the GM Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objectives

5.1.1.1 Primary Objective 1

5.1.1.1.1 Hypotheses

Equivalence of 3 MenACYW Conjugate Vaccine Lots in Terms of hSBA GMTs

Thirty days after the administration of the MenACYW conjugate vaccine, GMTs of antibodies against meningococcal serogroups A, C, Y, and W in Groups 1, 2, and 3 are equivalent.

Null hypothesis (H₀): $GMT_{(Gi)} / GMT_{(Gj)} \leq 1/2$ or $GMT_{(Gi)} / GMT_{(Gj)} \geq 2$ for any $i \neq j$

Alternative hypothesis (H₁): $1/2 < GMT_{(Gi)} / GMT_{(Gj)} < 2$ for all $i \neq j$

GMT_(Gi) and GMT_(Gj) are the GMTs of antibodies against the meningococcal serogroups A, C, Y, and W for the *i*th and *j*th lots, respectively.

Each of the antigens of A, C, Y, and W serogroups will be tested separately. If the 2-sided 95% confidence interval (CI) of the ratio of the GMTs is $> 1/2$ and < 2 for each pair of lots and each antigen, the non-equivalence assumption will be rejected (i.e. if the equivalence is demonstrated for each pair of lots).

5.1.1.1.2 Statistical Methods

Assuming that Log_{10} transformation of the data follows a normal distribution, the Log_{10} (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMTs.

For each of the equivalence hypotheses using the GMT ratios, the statistical methodology will be based on the use of the 2-sided 95% CI of difference in means of post-vaccination Log_{10} transformed titers between pairs of lots with normal approximation. Logarithm transformation of the individual post-vaccination titers will be calculated. Assuming that Log_{10} transformation of the data is normally distributed, the 95% CI for the difference in $\text{Log}_{10}(\text{GMT})$ between pairs of lots will be in the form:

$$\bar{X}_i - \bar{X}_j \pm t(1 - \alpha/2, n_i + n_j - 2) \cdot S \sqrt{1/n_i + 1/n_j}$$

where $\bar{X}_i = \log_{10}(\text{GMT})$ is the mean of $\log_{10}(\text{titer})$ of Group i ,

$S^2 = [(n_i - 1) S_i^2 + (n_j - 1) S_j^2] / (n_i + n_j - 2)$ is the pooled sample variance,

n_i and S_i^2 are the sample size and sample variance of Group i ,

$t(1 - \alpha/2, n_i + n_j - 2)$ is the 100(1- $\alpha/2$) percentile of the t -distribution with degrees of freedom $df = n_i + n_j - 2$.

Equivalence among the three lots will be demonstrated if, for each pair of lots and each antigen, the two-sided 95% CI for the difference in $\log_{10}(\text{GMT})$ lies between $\log_{10}(1/2)$ and $\log_{10}(2)$, or approximately -0.301 and 0.301.

5.1.1.2 Primary Objective 2

5.1.1.2.1 Hypothesis

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 percentages of subjects who achieve an hSBA vaccine seroresponse (as defined in Section 4.4.2.4) for meningococcal serogroups A, C, Y, and W in Groups 1, 2, and 3 combined are non-inferior to the corresponding percentages in Group 4.

Null hypothesis (H_0): $p_{(G123)} - p_{(G4)} \leq -10\%$

Alternative hypothesis (H_1): $p_{(G123)} - p_{(G4)} > -10\%$

where $p_{(G123)}$ and $p_{(G4)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse in Groups 1 - 3 pooled and Group 4, 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. The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

5.1.1.2.2 Statistical Methods

For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions will be computed for each of the serogroups A, C, Y, and W using the Wilson Score method without continuity correction (8).

Let $\hat{\theta} = p_{123} - p_4$, then $L = \hat{\theta} - \delta$ and $U = \hat{\theta} + \varepsilon$ are respectively the lower and the upper limits of the CI, where:

$$\delta = Z_{0.025} \sqrt{\left\{ \frac{l_{123}(1-l_{123})}{n_{123}} + \frac{u_4(1-u_4)}{n_4} \right\}}$$

$$\varepsilon = Z_{0.025} \sqrt{\left\{ \frac{l_4(1-l_4)}{n_4} + \frac{u_{123}(1-u_{123})}{n_{123}} \right\}}$$

l_{123} and u_{123} are calculated from the CI of the pooled proportion in Group 1 - 3 given by:

$$\frac{(2n_{123}p_{123} + Z_{0.025}^2 \pm Z_{0.025} \sqrt{(Z_{0.025}^2 + 4n_{123}p_{123}(1-p_{123}))})}{2(n_{123} + Z_{0.025}^2)}$$

l_4 and u_4 are calculated from the CI of the single proportion in Group 4 given by:

$$\frac{(2n_4p_4 + Z_{0.025}^2 \pm Z_{0.025} \sqrt{(Z_{0.025}^2 + 4n_4p_4(1-p_4))})}{2(n_4 + Z_{0.025}^2)}$$

where $Z_{0.025}$ is the upper 97.5th percentile of the standard normal distribution,

$n_{123} = n_1 + n_2 + n_3$ is the total sample size of Groups 1 - 3,

$p_{123} = \frac{\text{total \# of seroresponders in groups 1 - 3}}{n_{123}}$ is the overall seroresponse rate of

Groups 1 - 3.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Secondary Objective 1

5.1.2.1.1 Hypotheses

Non-inferiority of MenACYW Conjugate Vaccine Compared to Menactra[®] in Terms of hSBA Vaccine Seroresponse in the Adult Population (18 to 55 Years Old)

Thirty days after the administration of MenACYW conjugate vaccine or Menactra[®], the percentages of subjects who achieve an hSBA vaccine seroresponse (as defined in Section 4.4.2.4) for meningococcal serogroups A, C, Y, and W in Groups 1b, 2b, and 3b combined are non-inferior to the corresponding percentages in Group 4b.

Null hypothesis (H₀): $p_{(G123)} - p_{(G4)} \leq -10\%$

Alternative hypothesis (H₁): $p_{(G123)} - p_{(G4)} > -10\%$

where $p_{(G123)}$ and $p_{(G4)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse in Groups 1b, 2b, and 3b pooled and Group 4b, 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. The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

5.1.2.1.2 Statistical Methods

For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions will be computed for each of the serogroups A, C, Y, and W using the Wilson Score method without continuity correction (8). The statistical method as described in Section 5.1.1.2.2 will be used to Groups 1b - 3b pooled and Group 4b.

5.1.2.2 Secondary Objective 2

5.1.2.2.1 Hypotheses

Non-inferiority of MenACYW Conjugate Vaccine Compared to Menactra[®] in Terms of hSBA Vaccine Seroresponse in the Adolescent Population (10 to 17 Years Old)

Thirty days after the administration of MenACYW conjugate vaccine or Menactra[®], the percentages of subjects who achieve an hSBA vaccine seroresponse (as defined in Section 4.4.2.4) for meningococcal serogroups A, C, Y, and W in Groups 1a, 2a, and 3a combined are non-inferior to the corresponding percentages in Group 4a.

Null hypothesis (H₀): $p_{(G123)} - p_{(G4)} \leq -10\%$

Alternate hypothesis (H₁): $p_{(G123)} - p_{(G4)} > -10\%$

where $p_{(G123)}$ and $p_{(G4)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse in Groups 1a, 2a, and 3a pooled and Group 4a, 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. The overall non-inferiority of this objective will be demonstrated if all 4 individual null hypotheses are rejected.

5.1.2.2.2 Statistical Methods

For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions will be computed for each of the serogroups A, C, Y, and W using the Wilson Score method without continuity correction (8). The statistical method as described in Section 5.1.1.2.2 will be used to Groups 1a - 3a pooled and Group 4a.

5.1.2.3 Secondary Objective 3

Comparison of 3 MenACYW Conjugate Vaccine Lots in Terms of hSBA Vaccine Seroresponse

5.1.2.3.1 Hypotheses

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

5.1.2.3.2 Statistical Methods

The difference in percentages of subjects who achieve an hSBA vaccine seroresponse (as defined in Section 4.4.2.4) 30 days after the administration of MenACYW conjugate vaccine for meningococcal serogroups A, C, Y, and W in Groups 1, 2, and 3 will be calculated for each comparison and 95% CI will be provided.

The CI of the difference in proportions will be computed using the Wilson Score method without continuity correction (8).

5.1.2.4 Secondary Objective 4

Comparison of MenACYW Conjugate Vaccine to Menactra[®] in Terms of hSBA GMTs

5.1.2.4.1 Hypothesis

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

5.1.2.4.2 Statistical Methods

The ratio of GMTs of meningococcal serogroups A, C, Y, and W between the MenACYW conjugate vaccine Groups 1- 3 pooled (Lots 1, 2, and 3 combined) and the Menactra[®] Group 4 30 days after the administration of vaccine will be calculated and 95% CI will be provided.

Assuming that \log_{10} transformation of the data follows a normal distribution, the \log_{10} (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMTs.

For each of the GMT ratios, the statistical methodology will be based on the use of the 2-sided 95% CI of difference in means of post-vaccination \log_{10} transformed titers between the 2 groups with normal approximation.

The 95% CI for the difference in $\log_{10}(\text{GMT})$ between Group 1-3 pooled (Lots 1, 2, and 3 combined) and Group 4 will be in the form:

$$\bar{X}_{123} - \bar{X}_4 \pm t(1 - \alpha/2, n_{123} + n_4 - 2) \cdot S \sqrt{1/n_{123} + 1/n_4}$$

where $\bar{X}_i = \log_{10}(\text{GMT})$ is the mean of $\log_{10}(\text{titer})$ of Group i ,

$S^2 = [(n_{123} - 1) S_{123}^2 + (n_4 - 1) S_4^2] / (n_{123} + n_4 - 2)$ is the pooled sample variance,

n_i and S_i^2 are the sample size and sample variance of Group i ,

$t(1 - \alpha/2, n_{123} + n_4 - 2)$ is the $100(1 - \alpha/2)$ percentile of the t -distribution with degrees of freedom $df = n_{123} + n_4 - 2$.

The 95% CI for the ratio of GMTs can be obtained by taking antilog transformations for the calculated 95% CI for the difference in $\log_{10}(\text{GMT})$.

5.1.3 Statistical Methods for Observational Objectives

5.1.3.1 Hypothesis

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

5.1.3.2 Statistical Methods

5.1.3.2.1 Immunogenicity

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in each lot of MenACYW conjugate vaccine and in 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 (7). 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 GMTs and 95% CI at each time point for each group
- hSBA titer distribution and RCDC

- Proportion of subjects with hSBA titer $\geq 1:4$ and $\geq 1:8$ and 95% CI at D0 and D30 for each group
- Proportion of subjects with hSBA titer ≥ 4 -fold rise from pre-vaccination to post-vaccination, and 95% CI
- rSBA GMTs and 95% CI at each time point in a subset of 100 subjects in each group
- rSBA titer distribution and RCDC
- Proportion of subjects with rSBA titer $\geq 1:8$ and $\geq 1:128$ and 95% CI at D0 and D30 in a subset of 100 subjects in each group
- Proportion of subjects with rSBA titer ≥ 4 -fold rise from pre-vaccination to post-vaccination and 95% CI
- Vaccine seroresponse (as defined in Section 4.4.2.4) against meningococcal serogroups A, C, Y, and W measured by rSBA and 95% CI

5.1.3.2.2 Safety

Safety results in Section 4.3.2.2 will be described for subjects in all study groups. The main parameters for the safety endpoints will be described by 95% CIs (Clopper-Pearson method) (7). Analyses will contain at least the descriptions listed in Table 5.2:

Table 5.2: Statistical analyses for safety observational objective

Safety Events	Time and Group	Description
Immediate unsolicited systemic AE	Within 30 minutes after injection for all subjects in Groups 1 - 4 at D0	Proportion of subjects that have the event, MedDRA terms, intensity, relationship to vaccine, study discontinuation, duration
Solicited injection site reactions	Up to 7 days after D0 for all subjects in Groups 1 - 4	Proportion of subjects that have the event, time of onset, duration, intensity, action taken, study discontinuation, number of days of occurrence, temperature collection routes
Solicited systemic reactions	Up to 7 days after D0 for all subjects in Groups 1 - 4	
Unsolicited AE	Up to 30 days after D0 for all subjects in Groups 1 - 4	Proportion of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, study discontinuation
SAE	Up to 6-month follow-up after D0 for all subjects in Groups 1 - 4	Proportion of subjects that have the event, MedDRA terms, time of onset, duration, relationship, seriousness criteria, outcome, study discontinuation
MAAE	Between Visit 1 and Visit 2 for all subjects in Groups 1 - 4 (as unsolicited AE) From Visit 2 to 6-month follow-	Proportion of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, outcome, study discontinuation

	up contact for all subjects in Groups 1 - 4	
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5.1.4 Complementary Output

Additional analyses by age group, gender, and racial origin will be provided in Appendix 15 of the CSR.

Immunogenicity analyses:

- hSBA GMTs and 95% CI at each time point for each group – Per-Protocol Analysis Set
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA and 95% CI – Per-Protocol Analysis Set
- rSBA GMTs and 95% CI at each time point for each group – Per-Protocol Analysis Set
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by rSBA and 95% CI – Per-Protocol Analysis Set

Safety analyses:

- Safety overview after injection –Safety Analysis Set

Additional analyses will also be performed on SafAS2 with the following analyses:

- Safety overview after injection - Safety Analysis Set 2
- Unsolicited non-serious AEs in the six subjects at site [REDACTED] excluded from the Safety Analysis Set
- Solicited reactions in the six subjects at site [REDACTED] excluded from the Safety Analysis Set

Additional analyses will also be performed on PPAS2 and FAS2 with the following analyses:

- Equivalence of hSBA GMT against meningococcal serogroups A, C, Y, and W among 3 lots (Groups 1-3) 30 days after vaccination
- Non-inferiority of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine (Groups 1-3 pooled) versus Menactra® (Group 4)
- Non-inferiority of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine (Groups 1b-3b pooled) versus Menactra® (Group 4b)
- Non-inferiority of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine (Groups 1a-3a pooled) versus Menactra® (Group 4a)
- Difference of hSBA vaccine seroresponse rate against meningococcal serogroups A, C, Y, and W among 3 lots (Groups 1-3)
- Comparison of the hSBA GMT for MenACYW conjugate vaccine (Groups 1-3 pooled) versus Menactra® (Group 4)

5.2 Analysis Sets

Four analysis sets will be used: the Full Analysis Set (FAS), the Per-Protocol Analysis Set (PPAS), the Safety Analysis Set (SafAS), and the rSBA subset.

During the conduct of the study and before database lock, additional analyses sets (PPAS2, FAS2 and SafAS2) are added as needed and are detailed in each section.

5.2.1 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, i.e. a result different from not reportable (NR) or missing for at least one serogroup. All subjects will be analyzed according to the treatment group to which they were randomized.

Through data review and further investigation, it was found that at site [REDACTED] BL2 sample labels had been affixed to the sera samples collected during Visit 1, and BL1 labels were affixed to the Visit 2 sera sample. All 18 subjects from this site were incorrectly labeled and the investigation saw no other similar issues at other sites. Due to the mislabeling of sera samples at site [REDACTED], FAS2 will be defined the same as FAS but excluding all subjects from site [REDACTED].

5.2.2 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.

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

Due to the GCP quality issue related to safety data for six subjects [REDACTED], the safety data of these six subjects are regarded as not reliable, and they are excluded from the SafAS.

SafAS2 is defined the same as SafAS, but with adding those six subjects back into the safety analysis set.

5.2.3 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 (Visit 1, which is Day 0)
- Subject did not provide post-dose serology sample in the proper time window (Visit 2, which is 30 to 44 days after the vaccination at Visit 1) 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, i.e. a result different from 'NR' or missing for at least one serogroup (either pre or post-vaccination)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

Through data review and further investigation, it was found that at site [REDACTED], BL2 sample labels had been affixed to the sera samples collected during Visit 1, and BL1 labels were affixed to the Visit 2 sera sample. All 18 subjects from this site were incorrectly labeled and the investigation saw no other similar issues at other sites. Due to the mislabeling of sera samples at site [REDACTED], PPAS2 will be defined the same as PPAS but excluding all subjects from site [REDACTED] for the purpose of additional sensitivity analyses.

5.2.4 Other Analysis Set

rSBA subset

The rSBA subset is defined as those subjects who received the vaccine as per randomization and provided a valid post-vaccination rSBA result.

5.2.5 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.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

No replacement will be done. In all subject listings, partial and missing data will be clearly indicated as missing.

5.3.1.1 Immediate

For unsolicited non-serious systemic AEs, a missing response to the "Immediate" field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will be assumed to have occurred after the 30-minute surveillance period and will not be imputed. Such SAEs will not be considered as immediate.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.2 Immunogenicity

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

LLOQ and ULOQ management will be performed as described in Section 4.4.2.1.

The derived endpoint of fold-rise is computed for extreme values, to minimize the numerator and maximizes the denominator as in Section 4.4.2.3.

5.3.3 Efficacy

Not applicable.

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

5.5.1 Calculation of Sample Size

[REDACTED]

5.5.2 Power Calculation for the Primary Objectives

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

5.6 Data Review for Statistical Purposes

A blind review of the data has been anticipated through the data review process led by data management before database lock. This review of the data included a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

Not applicable

6 References List

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