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Title Page

Protocol Title:

A Phase III, open-label, single-center study to describe the immunogenicity and safety of a single dose of MenACYW Conjugate Vaccine in participants aged 12 months and older in Vietnam

Study Code: MEQ00074

Amendment Number: Not applicable

Compound: MenACYW Conjugate Vaccine (MenQuadfi™)

Short Title:

Study on a MenACYW Conjugate Vaccine administered as a single dose in participants aged 12 months and older in Vietnam

Study Phase: III

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information are provided in the Operating Guidelines.

The study centers, the Investigators at each center, and the Coordinating Investigator are listed in a separate document.

Document History

Not applicable as this is the first version of the protocol.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase III, open-label, single-center study to describe the immunogenicity and safety of a single dose of MenACYW Conjugate Vaccine in participants aged 12 months and older in Vietnam

Short Title:

Study on a MenACYW Conjugate Vaccine administered as a single dose in participants aged 12 months and older in Vietnam

Rationale:

The purpose of the MEQ00074 study will be to describe the immunogenicity and safety of a single dose of investigational quadrivalent Meningococcal Polysaccharide (serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in participants aged 12 months and older. The MenACYW conjugate vaccine is designed to cover broader age groups than those covered by Menomune-A/C/Y/W-135 and Menactra® vaccines. Menactra® vaccine has been used in routine programs in several countries since its licensure in 2005; it has been approved in Vietnam on 03 October 2018. However, the MenACYW conjugate vaccine is being developed by Sanofi Pasteur to ultimately replace Menactra® vaccine in the global market as a quadrivalent meningococcal conjugate vaccine indicated in infants/toddlers, children, adolescents, and adults.

Objectives and Endpoints:

Objectives	Endpoints
Immunogenicity	
• To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a single dose of MenACYW conjugate vaccine	Antibody titers against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) will be assessed before and 30 days after vaccination with a single dose of MenACYW conjugate vaccine.
Safety	
• To describe the safety profile of a single dose of MenACYW conjugate vaccine	The safety profile will be evaluated within 30 days (+14 days) after vaccination. The following endpoints will be used for the evaluation of safety:

Objectives	Endpoints
	• Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Presence of solicited (prelisted in the participant's diary card [DC] and case report form [CRF]) injection site and systemic reactions starting any time from the day of vaccination through 7 days after vaccination • Presence of unsolicited (recorded in a DC) non-serious AEs up to 30 days after vaccination; unsolicited non-serious AEs occurring after D31 will be presented in a specific listing • Presence of serious adverse events (SAEs) (including adverse events of special interest [AESIs]) throughout the study, ie from D01 (vaccination) to the last study day D31; SAEs occurring after D31 are also to be reported if they are considered related to vaccination with the investigational medicinal product (IMP) Depending on the items, the endpoints recorded or derived could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to the vaccine, whether the AE led to early termination from the study, outcome, and seriousness criterion

Overall Design

This is a Phase III, open-label, single-center study to describe the immunogenicity and safety of a single dose of MenACYW conjugate vaccine in participants aged 12 months and older in Vietnam.

Participants aged 18 years and above on the day of inclusion (adults), 10 to 17 years on the day of inclusion (adolescents), 2 to 9 years on the day of inclusion (children), and aged 12 to 23 months on the day of the inclusion (toddlers) will be eligible for enrollment in study MEQ00074.

All participants will receive a single dose of MenACYW conjugate vaccine on D01.

All participants will provide blood samples for immunogenicity assessments at baseline (pre-vaccination, Visit 1 on D01) and 1 month post vaccination on Visit 2 (D31 [+14 days]).

Solicited AE information will be collected for 7 days after vaccination (D01-D08); unsolicited AE information will be collected from Visit 1 (D01) to Visit 2 (D31 [+14 days]), and SAE information (including AESIs) will be collected throughout the study period.

Type of design	Single group, single-center
Phase	III
Control method	Uncontrolled
Study population	Meningococcal vaccination naïve, healthy toddlers, children, adolescents, adults and older adults aged 12 months and above
Country	Vietnam
Level and method of blinding	Open-label
Study intervention assignment method	Not applicable

Disclosure Statement:

This is a single group open-label study.

Number of Participants:

A total of 446 participants are expected to be enrolled with the aim to obtain a total of 400 evaluable participants:

- 223 participants will be 12-23 months of age
- 223 participants will be 24 months of age and above. To ensure all sub-groups are represented, a minimum of 20 participants will be enrolled from each of the sub-groups mentioned below:
  - Children 2 to 9 years of age
  - Adolescents 10 to 17 years of age
  - Adults 18 to 55 years of age
  - Older adults 56 years and above

Intervention Groups and Duration:

All eligible participants will receive a single intramuscular injection of MenACYW conjugate vaccine.

The duration of study participation for each participant will be approximately 30 to 44 days.

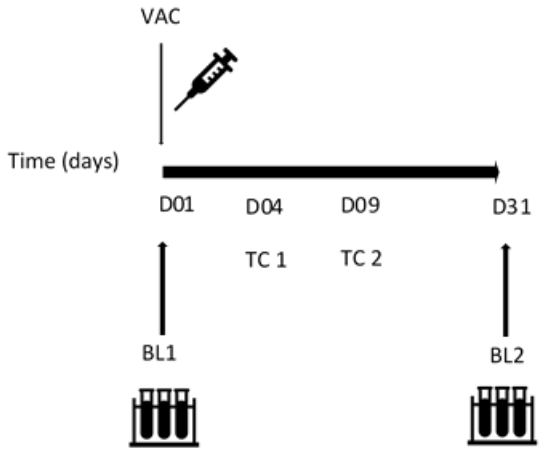
Data Monitoring/Other Committee:

Not applicable

1.2 Schema

The graphical design of MEQ000074 study is presented in Figure 1.1.

Figure 1.1 – Graphical study design



BL: blood sample; TC: telephone call; VAC: vaccination

1.3 Schedule of Activities (SoA)

Visit procedures are detailed in the Operating Guidelines.

Table 1.1: Schedule of activities

Phase III Study, 2 Visits, 2 Telephone calls, 1 Vaccination, 2 Blood Samples, 30 to 44 Days' Duration Per Participant

Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**TC1**	**TC2**	**Visit 2**
Study timelines (days)		D01	D04 Visit 1 + 3 days	D09 Visit 1 + 8 days	D31 Visit 1 + 30 days
Time windows (days)		-	+2 days	+2 days	+14 days
Visit procedures:					
Informed consent/assent*	X	X			
Inclusion/exclusion criteria	X	X			
Collection of demographic data	X	X			
Urine pregnancy test (if applicable)		X			
Collection of significant medical history	X	X			
Physical examination (including pre-vaccination temperature)**		X			
Review of temporary contraindications for blood sampling †	X				X
Blood sampling (BL) ‡ [3 mL]	X	BL0001			BL0002
Vaccination	X	X			
Immediate surveillance (30 min)	X	X			
Information on DC provided		X			
Telephone call (TC) §	X		X	X	
Collection of solicited injection site and systemic reactions**	X	Day 1 to Day 8			
Collection of unsolicited AEs	X	Visit 1 to Visit 2			
DC reviewed and information collected					X

Visit/Contact	*Collection of information in the CRF*	Visit 1	TC1	TC2	Visit 2
Study timelines (days)		D01	D04 Visit 1 + 3 days	D09 Visit 1 + 8 days	D31 Visit 1 + 30 days
Time windows (days)		-	+2 days	+2 days	+14 days
Visit procedures:					
Collection of reportable concomitant medications	X	X			X
Collection of SAEs, including AESIs ††	X	To be reported at any time during the study period			
Collection of pregnancies	X	To be reported at any time during the study period			
End of study participation record ‡‡	X				X

Abbreviations: AE: adverse event; AESI: adverse events of special interest; BL: blood sampling; CRF: case report form; DC: diary card; SAE: serious adverse event; TC: telephone call

* Assent required for participants aged 12 to 15 years.

**Physical examination should be performed as per standard of care. If a routine examination had been performed within the last week by the Investigator, a sub-Investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area. Temperature needs to be measured before vaccination and daily during the 7 days after vaccination and recorded in the DC.

†Should a participant receive oral or injectable antibiotic therapy within 3 days prior to any blood draw, the Investigator will postpone that blood draw until it has been 3 days since the participant last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw. 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 appropriately documented that the sample was taken less than 3 days after stopping antibiotic treatment.

‡Blood sample at Visit 1 to be drawn before administration of the vaccine.

§The first telephone call will be made 3 days to 5 days after the vaccination. The second telephone call will be made 8 days to 10 days after the vaccination. If Day 04 (+ 2 days) and Day 09 (+2 days) fall 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 participant experienced any SAE (including any AESI) not yet reported, and will remind the participant/participant's parent/legally acceptable representative to continue using the DC, bring the DC to the study center at the next visit, and confirm the date and time of the next visit.

** Solicited injection site and systemic reactions will be recorded from the day of vaccination through 7 days after vaccination.

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

‡‡ In case of participant discontinuation at a visit, the entire visit will be completed.

2 Introduction

The investigational quadrivalent Meningococcal Polysaccharide (serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) was 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 invasive meningococcal disease (IMD). Compared to a previous Sanofi Pasteur meningococcal conjugate vaccine, Menactra®, the MenACYW conjugate vaccine is prepared using tetanus toxoid as the carrier protein. Conjugation of polysaccharide antigens to a protein carrier can induce T-cell-dependent immune responses, which are anticipated to give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response.

The clinical development program targets licensure of the MenACYW conjugate vaccine in many countries in North America, Europe, Latin America, Africa, the Middle East, and Asia Pacific. It has been licensed for active immunization of individuals from 2 years of age in the United States (US) since April 2020, and for active immunization of individuals from 12 months of age in Canada and Australia since October 2020 and in the European Union (EU) since November 2020, under the brand name of MenQuadfi™. The MenACYW conjugate vaccine has also been recently approved in Brazil in individuals from 12 months of age.

MenACYW conjugate vaccine has been evaluated in over 7500 participants (infants, toddlers, adolescents, and adults) in completed Phase II and Phase III studies. In these studies, MenACYW conjugate vaccine was found to be well tolerated and did not reveal any apparent safety concerns with good immune responses non-inferior to comparators, for all 4 serogroups.

2.1 Study Rationale

According to regulations in Vietnam, local clinical trial data must be generated in order to obtain licensure in this country. MEQ00074 study will therefore generate immunogenicity and safety data of MenACYW conjugate vaccine in order to support registration in individuals 12 months of age and older in Vietnam.

MEQ00074 study will assess the immunogenicity and safety of a single dose of MenACYW conjugate vaccine administered to participants 12 months of age and older.

2.2 Background

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). Some age groups are disproportionately affected by IMD, with major peaks of IMD incidence occurring in infants, adolescents and young adults.

The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. IMD occurs worldwide in both endemic and epidemic forms with seasonal variation.

Clinical studies are ongoing to support an extension of the licensure in individuals from 6 weeks of age and older.

Although a surveillance and reporting system is in place in Vietnam, there is a paucity of IMD data. A serogroup C epidemic occurred in the Southern provinces of the country between 1977 and 1979. The overall incidence rate of meningococcal disease during the epidemic rose from < 5/100,000 in the preceding years to > 20/100,000. The mortality rate was between 27.4% and 34.7%. Seventy percent of cases occurred in children aged between 3 and 15 years. Four prospective studies of meningitis have been conducted since the 1977 epidemic covering the years 1993 to 2005. Between 2000 and 2002, the estimated incidence of meningococcal meningitis in Hanoi, Vietnam, was 21.8/100,000 (95% confidence interval [CI] 5.0–94.4) in children aged 7 to 11 months and 2.6/100,000 in children aged < 5 years (95% CI 0.8–8.5) (2). There have been sporadic serogroup C cases in Ho Chi Minh City (in 2006 and 2012). Serogroup B has been detected in IMD cases since 2012. A carriage study among military personnel in 2015 indicated carriage rates of 30-40% for serogroups B and C (3). Data are limited in Vietnam with regards to other serogroups.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events (AEs), the potential risks, and uncertainties of MenACYW conjugate vaccine may be found in the Investigator's Brochure (IB), Participant Information Leaflet, Package Insert, or Summary of Product Characteristics.

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.1.

Table 2.1: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: MenACYW conjugate vaccine		
Anaphylaxis	Known important risk occurring at a low frequency (very rare) based on what would be common for any vaccine. One case of anaphylaxis was reported 10 minutes after receiving the second dose of MenQuadfi™ given alone in study MET52. While temporal relationship was consistent with causal association to MenACYW conjugate vaccine and anaphylaxis has been reported with association to immunization in general, causality was assessed as related.	Observation period after vaccination for early detection and treatment. Exclusion criteria: Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study intervention used in the study or to a product containing any of the same substances.
Guillain-Barré syndrome	Important potential risk-based on post-marketing experience for other quadrivalent meningococcal conjugate vaccines occurring with a low frequency (very rare) with no definite evidence of excess risk identified in population based study (4) (5) (6). A review by the Institute of Medicine found inadequate evidence to accept or reject a causal relationship between tetanus toxoid-containing vaccines and Guillain-Barré syndrome (7). No cases with MenACYW conjugate vaccine in the completed studies.	Exclusion criteria: Personal history of Guillain-Barré syndrome
Bell's palsy Refer to IB Section 6 for more information regarding potential risks	Important potential risk-based on post-marketing experience for other quadrivalent meningococcal conjugate vaccines occurring at a low frequency (very rare).	No risk mitigation actions

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	A post-marketing observational safety study conducted in a US health maintenance organization found a statistically significant association with Bell's palsy when a licensed quadrivalent meningococcal conjugate vaccine (MCV4-CRM [Menveo®]) was administered concomitantly with other vaccines (tetanus, diphtheria, and acellular pertussis [Tdap], human papillomavirus [HPV], and/or influenza vaccine), while no association was found when the vaccine was administered alone (8). This study used a longer risk interval than used in previous studies, beyond the biologically plausible and widely accepted risk interval of 42 days. No cases with MenACYW conjugate vaccine within 42 days of vaccination in the completed studies.	
Study Procedures		
Vasovagal reactions (fainting)	Syncope can occur following, or even before, any vaccination or blood draw as a psychogenic response to the needle injection, most commonly in the adolescent age group (9). Cases of vasovagal-like response (eg, dizziness) or syncope have been observed infrequently in adolescent or young adult study participants within 30 minutes of vaccination with MenACYW conjugate vaccine.	Observation period after vaccination for early detection and treatment. Procedures should be in place to prevent falling injury and manage syncopal reactions.

2.3.2 Benefits from Study Participation

There might be no direct benefit from receiving MenACYW conjugate vaccine. However, based on the data from previous studies, evaluation of the immunogenicity profile of MenACYW

conjugate vaccine in different age groups shows that the majority of participants develop 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 the further evaluation of MenACYW conjugate vaccine in humans.

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

2.3.3 Coronavirus Disease 2019 Risk Assessment

MenACYW conjugate vaccine is a vaccine against IMD. MenACYW conjugate vaccine would not cause immune suppression. Therefore, the risk that a participant in this study will contract COVID-19 solely due to the administration of the study vaccine will be similar to the risk that a person not participating in this study will contract COVID-19. However, the risk of exposure to infected people cannot be completely excluded as the participants may need to be exposed to public areas (eg, commute to the site and at the site).

Risk mitigation for participants:

- Not start the study until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local Authorities.
- Continued risk assessment by the Investigator and Sponsor before deciding to start the study.
- Reduce the public exposure while ambulatory when possible.
- In order to limit the participant visits to the hospital, visits (blood draw, physical examination, safety assessments) may be conducted at the site (site visit) or at the participant's home (home visit). Implementation of home visits will be assessed based on the country situation, case-by-case situation and operational feasibility.

Risk mitigation for study management:

Remote source data verification and monitoring can be planned.

2.3.4 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, the potential risks that may result from study participation are balanced by the anticipated benefits that may be afforded to participants.

3 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 3.1.

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Immunogenicity	
• To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a single dose of MenACYW conjugate vaccine	Antibody titers against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) will be assessed before and 30 days after vaccination with a single dose of MenACYW conjugate vaccine.
Safety	
• To describe the safety profile of a single dose of MenACYW conjugate vaccine	The safety profile will be evaluated within 30 days (+14 days) after vaccination. The following endpoints will be used for the evaluation of safety: • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Presence of solicited (prelisted in the participant's diary card [DC] and case report form [CRF]) injection site and systemic reactions starting any time from the day of vaccination through 7 days after vaccination • Presence of unsolicited (recorded in a DC) non-serious AEs up to 30 days after vaccination; unsolicited non-serious AEs occurring after D31 will be presented in a specific listing • Presence of serious adverse events (SAEs) (including adverse events of special interest [AESIs]) throughout the study, ie from D01 (vaccination) to the last study day D31; SAEs occurring after D31 are also to be reported if they are considered related to vaccination with the investigational medicinal product (IMP) Depending on the items, the endpoints recorded or derived could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to the vaccine, whether the AE led to early termination from the study, outcome, and seriousness criterion

4 Study Design

4.1 Overall Design

This is a Phase III, open-label, single-center study to describe the immunogenicity and safety of a single dose of MenACYW conjugate vaccine in participants aged 12 months and older in Vietnam.

Participants aged 18 years and above on the day of inclusion (adults), 10 to 17 years on the day of inclusion (adolescents), 2 to 9 years on the day of inclusion (children), and aged 12 to 23 months on the day of inclusion (toddlers) will be eligible for enrollment in study MEQ00074.

All participants will receive a single dose of MenACYW conjugate vaccine on D01.

All participants will provide blood samples for immunogenicity assessments at baseline (pre-vaccination, Visit 1 on D01) and 1 month post vaccination on Visit 2 (D31 [+14 days]).

Solicited AE information will be collected for 7 days after vaccination (D01-D08); unsolicited AE information will be collected from Visit 1 (D01) to Visit 2 (D31 [+14 days]), and SAE information (including AESIs) will be collected throughout the study period.

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Single group, single-center
Phase	III
Control method	Uncontrolled
Study population	Meningococcal vaccination naïve, healthy toddlers, children, adolescents, adults and older adults aged 12 months and above
Level and method of blinding	Open-label
Study intervention assignment method	Not applicable

Number of participants	A total of 446 participants are expected to be enrolled with the aim to obtain a total of 400 evaluable participants:
	• 223 participants will be 12-23 months of age
	• 223 participants will be 24 months of age and above. To ensure all sub-groups are represented, a minimum of 20 participants will be enrolled from each of the sub-groups mentioned below:
	  • Children 2 to 9 years of age
	  • Adolescents 10 to 17 years of age
	  • Adults 18 to 55 years of age
	  • Older adults 56 years and above

Intervention groups	All eligible participants will receive a single intramuscular injection of MenACYW conjugate vaccine
Total duration of study participation	The duration of each participant's participation will be approximately 30 to 44 days
Country	Vietnam
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

4.2 Scientific Rationale for Study Design

The clinical development of MenACYW conjugate vaccine has started in 2006 with the objective to provide protection against 4 serogroups (A, C, Y, and W) that cause IMD, in all population age

groups, including infant as young as 6 weeks of age and including adults 56 years of age and older.

The initial licensures of this vaccine cover age 2 years and above in the US and age 12 months and above in Europe, Canada, Australia and Brazil, with a single injection. Studies are ongoing to support the extension of indication from 6 weeks of age.

The clinical studies supporting the first licensure were designed to demonstrate the ability of MenACYW conjugate vaccine to safely elicit a robust immune response. Studies were conducted to demonstrate efficacy through the non-inferiority of MenACYW conjugate vaccine compared to licensed meningococcal standard of care vaccines.

According to regulations in Vietnam, local clinical trial data must be generated in order to obtain licensure in this country.

4.3 Justification for Dose

All participants will receive a single dose of MenACYW conjugate vaccine on D01 as per the current/intended indication in this age group for quadrivalent meningococcal conjugate vaccines.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last visit planned in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:
I01: Aged 12 months and above on the day of inclusion

Adults (aged 18 and above on the day of inclusion):

I02: A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be pre-menarche[a] or post-menopausal for at least 1 year, or surgically sterile.

OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 4 weeks after study intervention administration.

A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine) within 1 week before the dose of study intervention.

I03: Informed consent form has been signed and dated

I04: Able to attend all scheduled visits and to comply with all study procedures

Adolescents (aged 10 to 17 years on the day of inclusion[b]):

I05: A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be pre-menarche[c].

OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 4 weeks after study intervention administration.

A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine) within 1 week before the dose of study intervention.

I06: Informed consent form has been signed and dated by both the participant (if aged 16 to 18 years) and the parent(s) or another legally acceptable representative and by an independent witness, if required by local regulations

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[a] Pre-menarche females will declare by themselves that they have not yet started menstruation. If a young female participant reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward

[b] "10 to 17 years" means from the day of the 10th birthday to the day before the 18th birthday

[c] Pre-menarche females will declare by themselves that they have not yet started menstruation. If a young female participant reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward

Assent form has been signed and dated by the participant (assent form required for participants aged 12 to 15 years) or verbal consent has been obtained (for participants aged 10 to 11 years), and informed consent form has been signed and dated by the parent(s) or another legally acceptable representative and by an independent witness, if required by local regulations

I07: Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

Children (aged 2 to 9 years on the day of inclusion[a]):

I08: Verbal consent has been obtained (for participants aged 7 to 9 years), and informed consent form has been signed and dated by the parent(s) or another legally acceptable representative and by an independent witness, if required by local regulations

I09: Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

Toddlers (aged 12 to 23 months on the day of inclusion[b])

I10: Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative and by an independent witness if required by local regulations

I11: Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

5.2 Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

Adults (aged 18 years and above), Adolescents (aged 10 to 17 years), Children (aged 2 to 9 years) and Toddlers (aged 12 to 23 months)

E01: Participation at the time of study enrollment (or in the 4 weeks preceding the study intervention administration) or planned participation during the present trial period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

E02: Receipt of any vaccine in the 4 weeks preceding the study intervention administration or planned receipt of any vaccine in the 4 weeks following study intervention administration except for influenza vaccination, which may be received at least 2

[a] "2 to 9 years" means from the day of the 2nd birthday to the day before the 10th birthday

[b] "12 to 23 months" means from the 12th month after birth to the day before the 25th month after birth

weeks before or after study vaccine. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

E03: Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (ie, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine)

E04: Receipt of immune globulins, blood or blood-derived products in the past 3 months

E05: History of any *N. meningitidis* infection, confirmed either clinically, serologically, or microbiologically

E06: At high risk for meningococcal disease during the study (specifically but not limited to participants with persistent complement deficiency, with anatomic or functional asplenia, or participants traveling to countries with high endemic or epidemic disease)

E07: Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study intervention used in the study or to a product containing any of the same substances[a]

E08: Personal history of Guillain-Barré syndrome

E09: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular injection

E10: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E11: Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[b]

E12: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (axillary temperature ≥ 37.5°C) or hypothermia (axillary temperature ≤ 35.5°C) on the day of vaccination. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E13: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

Adults (aged 18 years and above) and Adolescents (aged 10 to 17 years)

E14: 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

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[a] The components of MenACYW conjugate vaccine are listed in Section 6.1, and in Section 3 of the IB.

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders or chronic infection

(prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E15: Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within at least 10 years of the proposed study vaccination

E16: Self-reported thrombocytopenia, contraindicating intramuscular injection

E17: Alcohol, prescription drug, or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion

E18: Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

Children (aged 2 to 9 years)

E19: 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)

E20: Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine

E21: Thrombocytopenia as reported by the parent/legally acceptable representative, or suspected thrombocytopenia contraindicating intramuscular injection

E22: Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

Toddlers (aged 12 to 23 months)

E23: 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 since birth)

E24: Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine

E25: Thrombocytopenia as reported by the parent/legally acceptable representative, or suspected thrombocytopenia contraindicating intramuscular injection

E26: Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

If the participant has a primary physician who is not the Investigator, the site is recommended to

contact this physician with the participant's consent to inform him/her of the participant's participation in the study. In addition, the site may ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for the subsequent blood sample (on Visit 2) are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. Screening information is recorded in the source documents.

5.5 Criterion for Temporarily Delaying Enrollment

The reactogenicity of any of the COVID-19 vaccines available to date will occur during the first few days post-immunization. As immunogenicity interactions with other vaccines have not been studied, if the first dose of a COVID-19 vaccination is received before the participant is enrolled in the study, it is recommended to postpone enrollment at least 4 weeks after the last COVID-19 vaccine dose.

6 Study Intervention and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Note: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the CRF as reportable medications (see Section 6.8). Study procedures (eg, blood sampling) are also not considered as study interventions.

6.1 Study Intervention Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study intervention

Intervention Name	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Use	Investigational
IMP and NIMP	IMP
Type	Vaccine
Dose Formulation	Liquid solution
Unit Dose Strength(s)	Each dose of MenACYW conjugate vaccine contains the following components: Meningococcal capsular polysaccharides: • Serogroup A*: 10 µg • Serogroup C*: 10 µg • Serogroup Y*: 10 µg • Serogroup W*: 10 µg * Conjugated to tetanus toxoid protein carrier: 55 µg** ***Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation*
Excipients/Diluent	Sodium acetate buffered saline solution
Dosage Level	0.5 mL per dose
Number of Doses / Dosing Interval	1 dose
Route of Administration	Intramuscular injection
Site of Administration	Anterolateral area of the thigh or deltoid muscle
Sourcing	Provided by the Sponsor
Packaging and Labeling	MenACYW conjugate vaccine (single-dose vial) will be supplied with investigational labeling and packaging according to national regulations. Each single dose of study interventions will be identified by a unique number on the detachable label and on the outer carton label. The detachable label is for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.
Current/Former Name or Alias	MenQuadfi™
Batch Number	TBD
Storage Conditions	Study interventions will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The study interventions must not be frozen.

IMP: investigational medicinal product; NIMP: non-investigational medicinal product; TBD: to be determined

6.2 Preparation/Handling/Storage/Accountability

Detailed guidance and information are provided in the Operating Guidelines.

1) The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3) The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the Operating Guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

Participants will not be randomized.

6.3.2 Blinding and Code-breaking Procedures

This is a single-arm study that is not blinded.

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any non-compliance is documented so that it can be accounted for in the data analyses:

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

6.5 Dose Modification

Not applicable.

6.6 Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the Investigator should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for any AE/SAE
3) Document the quantity of the excess of the overdose in the source documents

6.8 Concomitant Therapy

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

Documentation in the CRF 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 include medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

This may include medications of interest that were started prior to the day of vaccination, and even stopped prior to enrollment if there is a reasonable possibility that they may have an impact on safety and/or immune assessment during study participation.

The following reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids [therapy duration less than 2 weeks] and other immune-modulators) Category 1 medications do not define the per-protocol analysis set (PPAS).

  Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.

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

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

- Category 2: medications impacting or that may have an impact on the immune response and used to define the PPAS; for example:
  - Flu vaccines administered 14 days (2 weeks) pre or post study intervention administration, including the day of the study vaccination visit.
  - Any vaccine other than the study vaccine and flu vaccines within the 4 weeks preceding or after the study vaccination, including the day of the study vaccination visit.
  - Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
  - Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) used in the 3 months preceding the study vaccination and up to the last blood draw, anti-cancer chemotherapy, anti-proliferative drugs such as deoxyribonucleic acid (DNA) synthesis inhibitors, or radiation therapy: used in the 6 months preceding the study vaccination, and up to the last blood draw

  Category 2 medications will be reported in the CRF according to the collection period detailed above up to the last blood draw.
- Category 3: medications impacting or that may have an impact on both the safety and the immune response: systemic (oral or injectable) antibiotics, received within 72 hours preceding each visit for blood draw related to investigational medicinal product (IMP) assessment (MenACYW conjugate vaccine) and used to define the PPAS, as they may interfere with bioassays used for antibody testing when taken before a blood draw

  Category 3 medications will be reported in the CRF for the period of 3 days (72 hours) before each blood draw.

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

Reportable medications (Category 1, 2, and 3) will be collected in the source document from the day of vaccination to the end of the study and in the CRF as per the instructions given below for each category.

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

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

[a] Medication prescribed for preventing AE occurrence (eg, paracetamol to reduce the risk of fever)

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded (except topical analgesics applied at the injection site of study intervention).

If the participant has received medications other than those listed in Categories 1, 2, and 3, the detailed information will be collected in the source documents only.

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

6.8.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available at the study site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.8.2 Coronavirus Disease 2019 Vaccine

If after study initiation coronavirus disease 2019 (COVID-19) vaccines become available for the population under study, the highest priority will be that study participants get their immunizations as per country recommendations.

Refer to Section 5.5 for the criterion for temporarily delaying enrollment in case of receipt of COVID-19 vaccine.

If a COVID-19 vaccine dose is received during one IMP solicited reactogenicity period it would not be possible to differentiate systemic reactions between the two. Likewise, if the vaccine is received between an IMP dose and the collection of blood, it will not be possible (at this point) to rule out an immunogenicity interaction. Therefore, in any of those two situations it is recommended that the participant be pulled out of the per protocol (PP) population but should continue in the trial within the intent-to-treat (ITT) population.

If the above observations would not apply, the participant could continue as PP.

The kind of COVID-19 vaccine received (including tradename) and the date time of its administration(s) should be documented in the concomitant medications CRF.

Wherever possible the site of injection of the IMP should be in the limb separate from the limb in which COVID-19 vaccine is administered (if it has already been administered). Likewise, and if on the control of the study site, any COVID-19 vaccine scheduled to be received after administration of the IMP should not be received in the same limb as the IMP. Where it is not possible to have the IMP and COVID-19 vaccine administered in separate limbs, a distance of at least 3.8 to 5.1 centimeters (1.5 to 2 inches) should be maintained between the two administration sites.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not applicable as there is only one vaccination.

7.2 Participant Discontinuation/Withdrawal from the Study

- Parents/legally acceptable representatives will be informed that they have the right to withdraw their child from the study at any time.
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: Adverse Event, Lost to Follow-up, Protocol Deviation, or Withdrawal by Participant or Parent/Legally Acceptable Representative.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any biological samples taken (unless local law requires not to destroy them), and the Investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, the site should attempt to contact them and complete all scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information. See Section 7.3 for definition of "lost to follow-up".

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Blood samples will be collected as described in the SoA table (Section 1.3). At Visit 1 (BL0001) and Visit 2 (BL0002), 3 mL of blood will be collected in tubes provided by or recommended by the Sponsor.

Guidance and information for the sample collection, preparation, storage, and shipment are provided in the Operating Guidelines.

8.1 Efficacy and Immunogenicity Assessments

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in a serum bactericidal assay utilizing the human complement (hSBA). Results will be expressed as antibody titer, geometric mean titers (GMTs), seroprotection and hSBA vaccine seroresponse.

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

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

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% carbon dioxide (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 quantification (LLOQ) of the hSBA assay is a titer of 1:4.

Assays will be performed at Global Clinical Immunology (GCI), Swiftwater, Pennsylvania, USA.

8.2 Safety Assessments

This section presents safety assessments other than AEs which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Medical History

Prior to enrollment, participants 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 participant 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 CRF. The significant medical history section of the CRF contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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

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

The reporting of signs and symptoms 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.

8.2.2 Physical Examinations

At Visit 1, the Investigator or a designee will perform a physical examination as per standard of care. Information will be recorded in the source document.

If a routine examination had been performed within the last week by the Investigator, a sub-Investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area.

8.2.3 Vital Signs

Pre-vaccination temperature will be systematically collected by the Investigator on the source document by axillary route. Tympanic, skin, and temporal artery thermometers must not be used.

8.2.4 Pregnancy Testing

Urine pregnancy testing will be performed in women of childbearing potential at Visit 1 before vaccination.

8.3 Adverse Events (AEs), Serious Adverse Events, and Other Safety Reporting

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.2.

AEs will be reported by the participants/participants' parents/legally acceptable representatives to the Investigator, then by the Investigator to the Sponsor.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.2.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Immediate Post-vaccination Observation Period

Participants 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.

Reactogenicity

Solicited injection site reactions will be collected from D01 to D08 after vaccination.

Solicited systemic reactions will be collected from D01 to D08 after vaccination.

The solicited injection site reactions and systemic reactions that are pre-listed in the DCs and CRF, together with the intensity scales, are presented in Appendix 10.2.5.1.1.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious AEs will be collected from D01 to D31 after vaccination. Unsolicited non-serious AEs occurring after D31 will be presented in a specific listing.

The intensity grading scale for unsolicited non-serious AEs is presented in Appendix 10.2.5.1.2.

Adverse Events of Special Interest (AESIs)

AESIs will be collected throughout the study period, from D01 to D31 after vaccination.

See Section 8.3.6 for the list of AESIs.

Serious Adverse Events

Information on SAEs will be collected and assessed throughout the study, from D01 until 30 days after vaccination. However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the CRF. In addition, SAEs occurring after D31 are also to be reported if they are considered related to vaccination with the IMP.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be recorded on the AE section of the CRF.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.2. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Individual DCs, 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. These DCs will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants/participants' 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 participants/participants' parents/legally acceptable representatives] on how to correctly use these tools.

At specified intervals, the Investigator or a designee will interview the participants/participants' parents/legally acceptable representatives to collect the information recorded in the DC, 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 designee using a web-based

CRF. Any information that was not documented in the DC will first be captured in the source document and then reported electronically.

The method of recording, evaluating, and assessing causal relationship of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant or parents/legally acceptable representatives refuses further contact. All AEs that are considered by the Investigator as serious, or related to the study intervention administered, or that led to study or vaccination discontinuation, or AESIs (as defined in Section 8.3.6), will be followed during the conduct of the study until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). For related SAEs ongoing at last study visit, such follow-up may need to continue after the end of the study.

Further information on follow-up procedures is provided in Appendix 10.2.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.
- An Investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5 Pregnancy

Pregnant women are not eligible to participate in the study and women of childbearing potential agree to use an effective contraceptive method, as defined in the inclusion criteria. However, a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery, by the Investigator, and recorded in the Pregnancy CRF.

Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.

- If a pregnancy is reported, the Investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit it to the Sponsor within 1 month of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 1 month beyond the estimated delivery date, but will be in accordance with local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

8.3.6 Adverse Events of Special Interest

An AESI is an event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. The following SAEs will be captured as serious AESIs throughout the study:

- Generalized seizures (febrile and non-febrile) (10)
- Kawasaki disease (11) (12) (13)
- Guillain-Barré syndrome (14)
- Idiopathic thrombocytopenic purpura (ITP) (15)

These events have been listed as AESIs based on the feedback received from the European Union regulators for the MenACYW conjugate vaccine.

No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in the completed clinical trials.

Because of their medical importance and to ensure expedited communication to the Sponsor, these AESIs are to be considered as SAEs and reported to the Sponsor according to the procedure

described in Appendix 10.2.4. Further instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

8.4 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are evaluated in this study.

8.7 Immunogenicity Assessments

See Section 8.1.2.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 Leftover Biological Samples and Use of Data

Any unused part of the biological samples collected for this study (blood 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, participants/participants' parents/legally acceptable representatives will be asked to indicate in the ICF whether they will permit the future use of any unused stored biological samples for other tests, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of any unused biological samples will not be included in the site-specific ICF). If they refuse permission, the biological samples will not be used for any testing other than that directly related to this study. If they agree to this future use, they will not be paid for giving permission. 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 and their mechanism of action, the knowledge of infectious diseases, or to improve existing tests or develop new tests to assess vaccines, or to help identify new vaccine targets or biomarkers that predict participant response to the vaccine. Such research may also include, but is not limited to, performing assessments on DNA, ribonucleic acid (RNA), proteins or metabolites. If future research on genetic material is performed, a specific individual consent will be obtained.

Data and samples will be used in compliance with the information provided to participants/participants' parents/legally acceptable representatives in the ICF Part 2 (future research). In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to the use of their biological samples or data for those research projects.

All study participant data and biological samples will be coded such that no direct identifiers will be linked to participants. Coded data and biological samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The biological samples will be securely stored at the Sponsor's facilities (R&D Global Operations, Swiftwater, Pennsylvania, USA) up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant/participants' parents/legally acceptable representatives request(s) destruction of the participant's samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and sample related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

Note: The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health during the study are dedicated for immediate use. If any of these biological samples are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

9 Statistical Considerations

Clinical data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor.

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

9.1 Statistical Hypotheses

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

Details on statistical methods are provided in Section 9.4.

9.2 Sample Size Determination

There are no statistically powered hypotheses in this study. No formal sample size calculations were performed.

A total of 446 participants will be enrolled in the study, 223 participants will be enrolled in age category 12 months to 23 months, 223 participants will be enrolled in age category 24 months and above. An estimated 10% non-adherence rate from enrollment will result in approximately 400 evaluable participants in total, and 200 evaluable participants in each age category (12 months – 23 months, ≥ 24 months).

The overall evaluable study cohort (N=400) will provide a probability of approximately 95% of observing any AE (at least 1 occurrence) with a true incidence of 0.75%.

For participants aged 12 to 23 months, 200 participants will provide a probability of approximately 95% of observing any AE (at least 1 occurrence) with a true incidence of 1.5%.

For participants aged 24 months and above, 200 participants will provide a probability of approximately 95% of observing any AE (at least 1 occurrence) with a true incidence of 1.5%.

9.3 Analysis Sets

The following populations are defined for immunogenicity and safety analyses:

Analysis Set	Description
Full analysis set (FAS)	Participants who received the study vaccine and had a valid post-vaccination serology result.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: • Participants did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant did not receive vaccine • Preparation and / or administration of vaccine was not done as per-protocol • Participants did not provide the post-dose serology sample at Visit 2 in the proper time window or a post-dose serology sample was not drawn • Participants received a category 2 or 3 protocol-prohibited therapy / medication / vaccine • Participants had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database. In addition to the reasons listed above, participants will also be excluded from the PPAS if their Visit 2 serology sample did not produce a valid test result. In the event of a local or national immunization program with a pandemic COVID-19 vaccine, participants who receive COVID-19 vaccine between an IMP dose and the collection of blood will not be withdrawn from the study, but will be excluded from PPAS.
Safety analysis set (SafAS)	Participants who have received the study vaccine and have any safety data available.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses than described in this section. This section is a summary of the planned statistical analyses of the most important endpoints.

9.4.1 General Considerations

Immunogenicity and safety parameters will be analyzed in specified analysis sets in the overall population, as well as by age categories (12 months – 23 months, ≥ 24 months).

The impact of COVID-19 pandemic situation on study conduct will be summarized through impact on visit procedures, study completion and major/critical protocol deviations due to COVID-19. The participants impacted by COVID-19 pandemic situation will be defined as the participants with at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19. If more than 10% of participants are impacted as per this definition, the main immunogenicity and safety endpoints will also be summarized in these participants to assess the impact of COVID-19 situation on study outcome.

9.4.2 Immunogenicity Endpoint

No statistical hypotheses will be tested. Descriptive statistics will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y by using hSBA before and 30 days after a single dose of meningococcal conjugate vaccine.

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS.

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 (16). For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log10-normally distributed.

Descriptive analyses of antibody responses to A, C, W, and Y serogroups using hSBA will include but not be limited to:

- GMTs and 95% CI.
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- Percentage of participants with titers ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of participants with hSBA titers ≥ 1:4 and ≥ 1:8, and 95% CI
- Percentage of participants with hSBA vaccine seroresponse, and 95% CI
  Note: hSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as:
  - For a participant with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16
  - For a participant with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

9.4.3 Safety Endpoints

No statistical hypotheses will be tested.

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

Depending on the items, the endpoints recorded or derived could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to the vaccine, whether the AE led to early termination from the study, outcome, and seriousness criterion.

All safety analyses will be performed on the SafAS.

9.5 Interim Analyses

No analyses are planned to be performed prior to the formal completion of the study.

9.6 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term “participant” is used throughout this protocol. However, the term “subject” will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements. Similarly, “legally acceptable representative” is used in the protocol whereas “guardian” is used in the CRF.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])

- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC [(in addition to summaries required from the Sponsor)]
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
    - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the Investigator's contract.

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her parent(s)/legally acceptable representative(s) and answer all questions regarding the study
- Participants must be informed that their participation is voluntary. Participants and their parents/legally acceptable representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center
- ICF may have to be signed and dated by an independent witness, if required by local regulations
- Participants aged 12 to 15 years will be required to sign an assent
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent/assent must also sign the ICF or AF.
- The actual ICF or AF used at each center may differ, depending on local regulations and IEC/IRB requirements. However, all versions must contain the standard information found in the sample ICF or AF provided by the Sponsor. Any change to the content of the ICF or AF must be approved by the Sponsor and the IEC/IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's or parents'/legally acceptable representatives' willingness to continue participation in the study, this will be communicated to him/her in a timely manner. Such information will be provided via a revised ICF or AF or an addendum to the original ICF or AF.
- Participants and their parents/legally acceptable representatives must be re-consented to the most current version of the ICF or AF during their participation in the study.
- A copy of the ICF or AF must be provided to the participant or their parents/legally acceptable representatives.

Rationale for Including Participants Unable to Give Consent:

MEQ00074 is a study to be conducted in participants aged 12 months and older; its aim is to obtain immunogenicity and safety data in participants who are meningococcal vaccination naïve.

Since minor participants are unable to give their consent, written informed consent must be obtained from the parent(s) or legally acceptable representative in accordance with local practices before participation in the study and before any study-related procedure is done. The signature on the ICF must be dated by the parent(s)/legally acceptable representative in accordance with local

practices. The parent/legally acceptable representative should be able to consent for their child. The child of minor parents must not be included in the study.

Recruitment Procedure

An appropriate pool of potential participants (independent of the Investigator and investigational team) will be approached during their routine visit to the investigational site. The Investigator/investigational team at the study site will take the responsibility of participant recruitment. The site will ensure that any advertisements used to recruit participants (letters, pamphlets, posters, etc.) are submitted to the IEC/IRB for approval.

10.1.4 Data Protection and Future Use of Stored Samples

- All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. 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.
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant/parent(s)/legally acceptable representative must be informed that the participant's personal study-related data will be used by the Sponsor in accordance with applicable data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant/parent(s)/legally acceptable representative must be informed that the participant'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 participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data will be used for this study and in support of the whole drug development program for the Investigational Product, including negotiations with payers and publication of results.
- Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) up to 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.

The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health are dedicated for immediate use. In case they are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

In addition, parent(s)/legally acceptable representative 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.

10.1.5 Committees Structure

This study will not include an early safety data review.

10.1.6 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations [CROs]).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Remote site visits may be planned in case the COVID-19 pandemic situation does not allow to go on site.
- Records and documents, including signed ICFs and AFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. 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.

10.1.8 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, DCs, medical and hospital records, screening logs, ICFs or AFs, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Detailed guidance and information are provided in the Operating Guidelines.

10.1.9 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the Operating Guidelines.

The study start date is considered the date of the first visit planned in the SoA of the first participant. The study end date is considered as the site closure date.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the center study-site has all the documents necessary for archiving and a study-site closure visit has been performed along with a Site Close Out Form submitted to the IRB, as required.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants by the Investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(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 participant/parent(s)/legally acceptable representative and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Information related to publication policy is described in the Investigator’s contract.

10.2 Appendix: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

All noxious and unintended responses to a study intervention related to any dose should be considered adverse reactions (ARs).

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

Immediate Event/Reaction:

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

Injection Site Reaction/Administration Site Reaction:

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

Systemic Adverse Event/Adverse Reaction:

Systemic ARs are all ARs 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 injection or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Systemic AEs assessed as related to study intervention are referred as systemic ARs.

Adverse Event of Special Interest:

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

Reactogenicity / Solicited Reactions

A solicited reaction is an "expected" AR (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF.

By definition, solicited reactions are considered as being related to the study intervention administered.

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

Unsolicited Adverse Event/Adverse Reaction:

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (eg, headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to the study intervention administered.

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

10.2.2 Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An Serious Adverse Event is defined as any adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Is other medically important event

- Medical or scientific judgment should be exercised by the Investigator in deciding whether expedited reporting is appropriate in other situations such as significant medical events that may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious. These include generalized seizures (febrile and non-febrile), Kawasaki disease, Guillain-Barré syndrome, and ITP (see Section 8.3.6).
- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization, or development of drug dependency or intervention abuse, new-onset diabetes or autoimmune disease.

Note: *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 participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.2.3 Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

By convention, all AEs reported at the injection site (either solicited or unsolicited) and all solicited systemic AEs are considered to be related to the study intervention (see definition in Section 6) and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the Investigator only.

- For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the Global Pharmacovigilance (GPV) database only.
- For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.

- The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered[a] a 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 participants' 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 study intervention administered, meaning that there are facts (evidence) or arguments to suggest a causal relationship
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

[a] Study intervention administered can correspond to either the investigational product or other products when no investigational product is administered at the visit

Follow-up of Adverse Events and Serious Adverse Events
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, when available the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information. • AEs likely to be related to the study intervention, 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 participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.2.4 Reporting of Serious Adverse Events

Serious Adverse Event Reporting to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section). • Details regarding SAE reporting can be found in the Operating Guidelines.

Serious Adverse Event Reporting to the Sponsor via Paper Case Report Form
The SAE paper CRF can be sent to the Sponsor by one of the following means: • By fax, to the following number: 001-570-957-3172 • In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com (see the Operating Guidelines for directions on how to send a password-protected e-mail).

- By express mail, to the following address:

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

Safety Emergency Call

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

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

10.2.5 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the "Food and Drug Administration (FDA) Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

10.2.5.1 Tables for Clinical Abnormalities

10.2.5.1.1 Solicited AR Intensity Grading Scale

Table 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales – Infants and toddlers aged ≤ 23 months

CRF term (MedDRA lowest level term [LLT])	**Injection site tenderness**	**Injection site erythema**	**Injection site swelling**
Diary card term	Tenderness	Redness	Swelling
Definition	Pain when the injection site is touched or injected limb mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3 (**CRF**): Cries when injected limb is mobilized, or the movement of the injected limb is reduced Grade 3 **(diary card)**: Cries when injected limb is moved or the movement of the injected limb is reduced	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

MedDRA: Medical Dictionary for Regulatory Activities

* For tenderness, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grade 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 10.2: Solicited injection site reactions: terminology, definitions, and intensity scales – Children aged 2 through 11 years

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	**CRF:** Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents 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

MedDRA: Medical Dictionary for Regulatory Activities

* For pain, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 10.3: Solicited injection site reactions: terminology, definitions, and intensity scales – Adolescents and adults aged ≥ 12 years

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

MedDRA: Medical Dictionary for Regulatory Activities

* For pain, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 10.4: Solicited systemic reactions: terminology, definitions, and intensity scales – Infants and toddlers aged ≤ 23 months

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥ 38.0°C	Vomiting does not include spitting up	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.5°C	Grade 1: 1 episode per 24 hours	Grade 1: < 1 hour	Grade 1: Sleepier than usual or less interested in surroundings	Grade 1: Eating less than normal	Grade 1: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C	Grade 2: 2–5 episodes per 24 hours	Grade 2: 1–3 hours	Grade 2: Not interested in surroundings or did not wake up for a feed / meal	Grade 2: Missed 1 or 2 feeds / meals completely	Grade 2: Requiring increased attention
	Grade 3: > 39.5°C	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	Grade 3: Inconsolable

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, 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.

Table 10.5: Solicited systemic reactions: terminology, definitions, and intensity scales – Children aged 2 through 11 years, adolescents or adults aged ≥ 12 years

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C	**CRF:** 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.	**CRF:** 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.	**CRF:** 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.

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
	Grade 2: ≥ 38.5°C to ≤ 38.9°C	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	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.
		Diary card:	**Diary card:**	**Diary card:**
		Grade 1: No interference with usual activities	Grade 1: No interference with usual activities	Grade 1: No interference with usual activities
		Grade 2: Some interference with usual activities	Grade 2: Some interference with usual activities	Grade 2: Some interference with usual activities
		Grade 3: Significant; prevents usual activities	Grade 3: Significant; prevents usual activities	Grade 3: Significant; prevents usual activities

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, 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:

Participants or participants' parents/legally acceptable representatives are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is axillary.

10.2.5.1.2 Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.2.5.1.1).

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

- Grade 1
  - CRF: 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.
  - DC: No interference with usual activities.
- Grade 2
  - CRF: 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.
  - DC: Some interference with usual activities.
- Grade 3
  - CRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - DC: Significant; prevents usual activities.

10.3 Appendix: Contraceptive and Barrier Guidance

10.3.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1) Premenarchal
2) Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3) Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c) [Male condoms must be used in addition to hormonal contraception].
d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
e) Male condom and female condom should not be used together (due to risk of failure from friction).

10.4 Appendix: Risk-based Approach

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.5 Appendix: Abbreviations

AE	Adverse event
AF	Assent form
AESI	Adverse event of special interest
AR	Adverse reaction
BL	Blood sample
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract Research Organization
DC	Diary card
DNA	Deoxyribonucleic acid
EU	European Union
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	Geometric mean titer
GPV	Global Pharmacovigilance
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papillomavirus
HRT	Hormonal replacement therapy
hSBA	Serum bactericidal assay using human complement
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMD	Invasive meningococcal disease

IMP	Investigational medicinal product
IRB	Institutional Review Board
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
LLOQ	Lower limit of quantification
MCV4-CRM	Meningococcal conjugate vaccine quadrivalent
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-investigational medicinal product
NSAID	Non-steroidal anti-inflammatory drug
PP	Per protocol
PPAS	Per-protocol analysis set
RCDC	Reverse cumulative distribution curve
RMO	Responsible Medical Officer
RNA	Ribonucleic acid
SAE	Serious adverse event
SafAS	Safety analysis set
SAP	Statistical analysis plan
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TC	Telephone call
Tdap	tetanus, diphtheria, and acellular pertussis
US(A)	United States (of America)
WOCBP	Woman of Childbearing Potential

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12 Sponsor Signature Page

Signature Page for VV-CLIN-0607397 v1.0
MenQuadTT-MEQ00074-protocol-version1.0

Approve & eSign	[redacted] Clinical 01-Apr-2021 02:11:40 GMT+0000