Clinical Study Protocol

Protocol Title:

A descriptive, Phase IV, open-label, single-arm multi-center study to assess the immunogenicity and safety of MenQuadfi® as a booster vaccine in healthy toddlers 12 to 23 months of age who had been primed with at least 1 dose of another quadrivalent meningococcal conjugate vaccine, ie, Nimenrix® (MCV4-TT) or Menveo® (MCV4-CRM), in infancy.

Study Code: MEQ00086

Amendment Number: Not applicable

Compound: MenQuadfi®

Brief Title:

Study of immunogenicity and safety of MenQuadfi® as a booster vaccine in toddlers 12 to 23 months, regardless of the quadrivalent meningococcal conjugate vaccine used for priming in infancy.

Study Phase: Phase IV

Sponsor Name and Legal Registered Address:

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Manufacturer:

Sanofi Pasteur Inc.
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Regulatory Agency Identifier Number:

WHO UTN: U1111-1277-6838

Protocol Version Number: 2.0

Approval Date: 03 February 2023

Responsible medical officer (RMO), and designee(s), and pharmacovigilance (PV) representative names and contact information will be provided separately.

The study center(s), the investigators at each center, and the coordinating investigator(s) are also listed in a separate document.

Document History

Previous Version	Date	Comments
1.0	27 September 2022	Version submitted to IRB/IEC and was updated (to version 2.0) per review comments. Version 1.0 was not used in the study

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:

A descriptive, Phase IV, open-label, single-arm multi-center study to assess the immunogenicity and safety of MenQuadfi® as a booster vaccine in healthy toddlers 12 to 23 months of age who had been primed with at least 1 dose of another quadrivalent meningococcal conjugate vaccine, ie, Nimenrix® (MCV4-TT) or Menveo® (MCV4-CRM), in infancy.

Brief Title:

Study of immunogenicity and safety of MenQuadfi® as a booster vaccine in healthy toddlers 12 to 23 months, regardless of the quadrivalent meningococcal conjugate vaccine used for priming in infancy.

Rationale:

The objective of MEQ00086 study is to describe the immunogenicity and safety of MenQuadfi® (Meningococcal Polysaccharide [Serogroups A, C, Y, and W] Tetanus Toxoid (TT) Conjugate Vaccine, also identified as MenACYW conjugate vaccine or as MenACYW-TT) when administered as a booster dose in healthy toddlers 12 – 23 months of age who had been primed during the first year of life with at least 1 dose of another licensed quadrivalent meningococcal conjugate vaccine, either Nimenrix® (MCV4-TT) or Menveo® (MCV4 - CRM). The evidence generated from this study will provide reassurance that MenQuadfi® used as a booster dose in toddlers who had been primed with another licensed MCV4 vaccine will provide an adequate immune response and protection against invasive meningococcal disease (IMD).

Objectives, Endpoints:

Objectives	Endpoints
Immunogenicity	**Immunogenicity**
1) To describe the immune response to a booster dose of MenQuadfi® as measured by the serum bactericidal assay using human complement (hSBA) in toddlers aged 12-23 months, who had been primed with at least 1 dose of another MCV4 vaccine during infancy 2) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of	1) hSBA antibody titers ≥ 1:8 (seroprotection) against meningococcal serogroups A, C, W and Y at D31 (+14 days) after booster vaccination with MenQuadfi® 2) At Day (D)01 (baseline) before vaccination and at D31 [+14 days] after the administration of a booster dose of MenQuadfi® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by hSBA:

MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy
 	
3) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with 2 doses of another MCV4 vaccine during infancy
 	
4) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with 1 dose of another MCV4 vaccine during infancy
 	
5) To describe the antibody responses to tetanus toxoid before and 1 month after a booster dose of MenQuadfi® in toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy
	• Antibody titers against meningococcal serogroups A, C, W, and Y
	• Antibody titers ≥ 1:4 and ≥ 1:8
	• ≥ 4-fold rise from pre-vaccination to post-vaccination
	• Vaccine seroresponse, defined as follows:
	  • For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16
	  • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer
	
	At Day (D)01 (baseline) before vaccination and at D31 [+14 days] after the administration of a booster dose of MenQuadfi® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by rSBA:
	• Antibody titers against meningococcal serogroups A, C, W, and Y
	• Antibody titers ≥ 1:8 and ≥ 1:128
	• ≥ 4-fold rise from pre-vaccination to post-vaccination
	• Vaccine seroresponse defined as follows:
	  • For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32
	  • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer
	
	3) Same endpoints as described for endpoint #2
	
	4) Same endpoints as described for endpoint #2
	
	5) Antibody concentrations against tetanus toxoid at D01 (baseline) and at D31 (+14 days) after the administration of a booster dose of MenQuadfi®

Safety	**Safety**
• To describe the safety profile of a booster dose of MenQuadfi® administered to toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy	• Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination. • Presence of solicited (pre-listed in the participant's diary card [DC] and case report form [CRF]) injection site reactions up to 7 days after vaccination. • Presence of solicited systemic reactions (pre-listed in the participant's DC and CRF) up to 7 days after vaccination. • Presence of unsolicited AEs up to 30 days after vaccination. • Presence of serious adverse events (SAEs) [including AESIs], throughout the trial from Visit 1 to 30 days after study vaccination. 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 descriptive, Phase IV, open-label, single-arm, un-controlled, multi-center study to describe the immunogenicity and safety of a single dose of MenQuadfi® administrated as a booster vaccine in healthy toddlers 12 – 23 months of age who had been primed before study participation with at least 1 dose of another quadrivalent meningococcal conjugate vaccine, ie, Nimenrix® (MCV4-TT) or Menveo® (MCV4-CRM), in infancy.

The eligible participant population for this booster vaccine administration will be recruited in Argentina from the general population who have received at least one of the 2 infant doses of quadrivalent meningococcal conjugate vaccine (Nimenrix® or Menveo®) recommended at 3-months or at 5-months of age.

All participants will receive a single booster dose of MenQuadfi® at Visit 1 on Day (D)01.

All participants will provide a 5 mL blood sample for immunogenicity assessments at D01, pre-vaccination (baseline) and 1-month post booster vaccination at D31 (+14 days).

Solicited AE information will be collected for 7 days after booster vaccination; 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 from D01 to D31 (+14 days) after booster vaccination.

Type of design	Open-label, single-group, multi-center
Phase	IV
Control method	Un-controlled
Study population	Healthy toddlers aged 12 months to 23 months
Countries	Argentina
Level and method of blinding	open-label
Study intervention assignment method	No randomization

Brief Summary:

This study will evaluate the immunogenicity and safety of a single dose of MenQuadfi® administered as a booster vaccine in toddlers 12 – 23 months of age in Argentina who had been primed with at least 1 dose of the quadrivalent meningococcal conjugate vaccines Nimenrix® or Menveo® during infancy to protect against IMD.

Study Duration: Approximately 1 month per participant.

Treatment Duration: Participants will receive a single dose of MenQuadfi® at Visit 1. Participants will provide 2 blood samples, one at D01 (Visit 1) pre-vaccination and another at D31 (Visit 2) post-vaccination for the immunogenicity assessments.

Visit Frequency: Study will include 2 visits at D01 (Visit 1) and at D31 (Visit 2), and 1 Telephone call (TC) for safety follow-up at D09 post study vaccination.

Number of Participants:

A total of approximately 180 participants (minimum of 30 evaluable participants from the low - enrolling of the 2 priming vaccines) are expected to be enrolled with the aim to obtain a total of 150 evaluable participants.

Intervention Groups and Duration:

Eligible participants (12 – 23-month-old toddlers who had received at least one of two priming doses of either Nimenrix® or Menveo® vaccine during infancy as part of their routine immunization, before 12 months of age) will be assigned in an open-label design to receive a single booster dose of MenQuadfi® vaccine with an interval of at least 2 months after the last vaccination with Nimenrix® or Menveo®, as an intramuscular (IM) injection at D01.

The duration of participation will be approximately 1 month for each participant.

Study Intervention:

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

- Form: Liquid solution

- Composition: Each 0.5 milliliter (mL) dose of MenACYW conjugate vaccine was formulated in sodium acetate buffered saline solution to contain the following ingredients:

Meningococcal capsular polysaccharides:

- Serogroup A 10 µg
- Serogroup C 10 µg
- Serogroup Y 10 µg
- Serogroup W 10 µg

Tetanus toxoid protein carrier approximately 55 µg*

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

- Route of administration: Intramuscular (IM) injection

Statistical Considerations:

All analyses will be descriptive; no hypotheses will be tested.

In general, categorical variables will be summarized and presented by frequency counts, proportion percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the Exact binomial distribution (Clopper-Pearson method) for percentages. For geometric mean titers (GMTs), 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

For immunogenicity data, assuming that log10 transformation of the titers / concentrations follows a normal distribution, first, the mean and 95% confidence intervals (CIs) will be calculated on log10 (titers / concentrations) using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, to compute geometric mean titers / concentrations (GMTs / GMCs) and their 95% CIs.

All immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS) and presented overall and by priming vaccine. Additional immunogenicity analyses will be performed on the full analysis set (FAS). Descriptive statistics will be provided for the hSBA and rSBA antibody titers against meningococcal serogroups (A, C, W, and Y) and for antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine as a carrier protein.

Safety analyses will be performed on the Safety Analysis Set (SafAS) and presented overall and by priming vaccine. The main parameters for the safety endpoints will be described by 95% CIs using the Exact binomial method (Clopper-Pearson method).

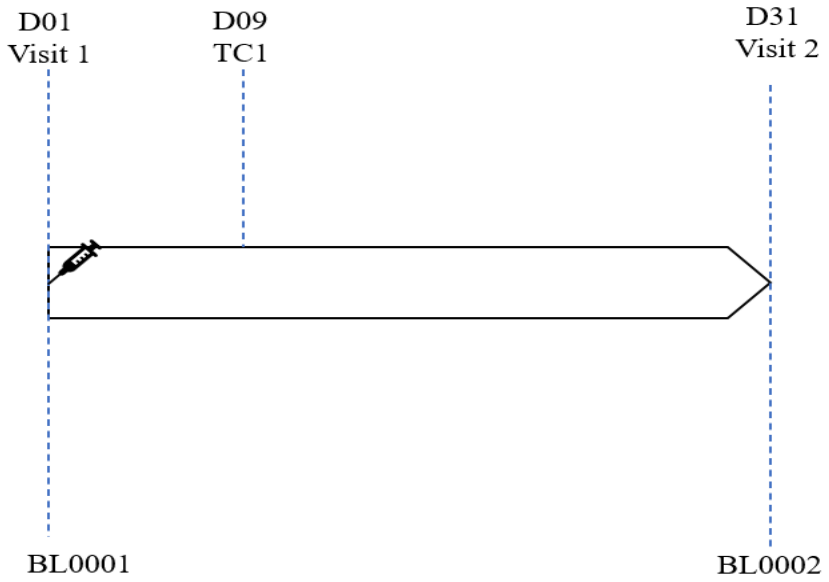
Data Monitoring/Other Committee:

No

1.2 SCHEMA

The graphical design of MEQ00086 study is presented in Figure 1.

Figure 1 – Graphical study design



BL: blood sample
BL0001 (pre-vaccination) and BL0002 for immunogenicity assessments

D: day; TC: telephone call;

D09 TC1: Day 09 safety follow up

: Vaccination

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1.1: Schedule of activities

Phase IV Study, 2 Visits, 1 Vaccination, 2 Blood Samples, ~1 Month Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	TC1§	Visit 2**
Study timelines (days)		D01	D09	D31
Time windows (days)		NA	[+2 D]	[+14 D]
Visit procedures:				
Informed consent	X	X		
Inclusion/exclusion criteria	X	X		
Collection of demographic data	X	X		
Collection of Medical history	X Significant Medical History	X		
Collection of vaccination history	X	X		
Physical examination		X		X
Pre-vaccination temperature		X		
Review of temporary contraindications for blood sampling*	X	X		X
Allocation of participant number	X	X		
Blood sampling (BL)† [5 mL]	X	BL0001 Pre-vac		BL0002
Vaccination (vac)	X	X		
Immediate surveillance (30 min)	X	X		
Diary card provided		X		
Collection of solicited injection site and systemic reactions	X	X	X	
Collection of unsolicited adverse events (AEs)	X	X	X	X
Diary card collected				X
Collection of concomitant medications	X Reportable concomitant medication	X	X	X
Collection of SAEs, including adverse events of special interest (AESIs)	X	To be reported at any time during the study from D01 to D31 (+14 days) after study vaccination		
End of Active Phase participation record‡	X			X

AESI: Adverse Events of Special Interest; CRF: case report form; SAE: Serious Adverse Events

* Should a participant receive oral or injectable antibiotic therapy within 3 days prior to each 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 is still to be within the timeframe for blood draw (30 to 44 days after vaccination at D01). If postponement will result in the sample collection falling outside of the appropriate timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment

† Blood sample at D01 will be drawn before administration of the vaccine

‡In case of participant discontinuation at a visit, the entire visit will be completed. Active Phase is from Visit 1 to Visit 2 completion.

§ The Investigator or an authorized designee will remind the parents, guardians, or legally acceptable representatives to bring back the diary card (DC) at the next visit and will answer any questions. If D09 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAEs (including AESIs) not yet reported and will remind the subject's parent/guardian to continue using the diary card, to bring the diary card to the study center at the next visit and confirm the date and time of the next visit.

**The Investigator or an authorized designee will interview the parents, guardians, or legally acceptable representatives to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

2 INTRODUCTION

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

The goal for the MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, W, and Y in all age groups including children as young as 6 weeks of age, adolescents, and adults, including those 56 years of age and older. Clinical studies are ongoing to support an extension of the licensure in individuals from 6 weeks of age and older.

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 in the European Union (EU) since November 2020. The MenACYW conjugate vaccine has also been approved in Argentina (May 2021) in individuals from 12 months of age.

MenACYW conjugate vaccine has been evaluated in over 7500 participants (infants, toddlers, adolescents, and adults, including those > 56 years of age) in completed Phase II and Phase III studies. In these studies, the MenACYW conjugate vaccine was found to be well tolerated and did not reveal any apparent safety concerns. Phase III studies are ongoing to investigate the vaccine in infants from 6 weeks of age.

2.1 STUDY RATIONALE

The objective of MEQ00086 study is to describe the immunogenicity and safety of the MenACYW conjugate vaccine when administered as a booster dose in healthy toddlers 12 – 23 months of age who had been primed during the first year of life with at least 1 dose of another licensed quadrivalent meningococcal conjugate vaccine, either Nimenrix® (MCV4-TT) or Menveo® (MCV4-CRM), according to the immunization practices in Argentina. The purpose is to demonstrate that the MenACYW conjugate vaccine booster vaccination will elicit a strong immune response in toddlers who had been primed with either Nimenrix® or Menveo®. The evidence generated from this study may provide assurance that the MenACYW conjugate vaccine used as a booster dose in toddlers primed with another licensed MCV4 may provide adequate immune response and protection against IMD.

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. At least 12 distinct meningococcal serogroups have been classified based on the immunochemistry of the capsular polysaccharides (PS). Some strains are more likely than others to cause infection. Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (2) (3) (4).

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

A retrospective observational study based on four Argentinean national databases (National Surveillance system, hospital, vital statistics, and laboratory network) reported an average number of IMD cases of up to 450 per year between 2007 to 2016, after adjusting by improved bacterial culture methods and PCR, and a mean mortality rate of 0.098 per 100 000 habitants. The percentage of the two most common serogroups, B and W represented together an average of 89% of all cases of *N. meningitidis* infections characterized by the National Reference Laboratory between 2008 and 2016. The peak number and incidence rates of estimated IMD cases occurred in the age group <1 year, followed by the age group 1 to 4 years (5). It is estimated that the incidence declined from 0.75/100,000 in 2012 to 0.28/100,000 in 2016. There has not been new data published since 2017, when the MenACWY conjugate vaccine was introduced in the National Immunization Program (NIP) for infants at 3, 5 and 15 months, with a dose for adolescents at 11 years of age (6).

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 (7) (8) (9). 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 (10). 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	No risk mitigation actions

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	vaccines occurring at a low frequency (very rare). 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 (11). 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 (12). 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 COVID-19 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 trial will contract COVID solely due to the administration of the study intervention(s) will be similar to the risk that a person not participating in this trial will contract COVID. 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/from the site and at the site).

Risk Mitigation:

- 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 trial.
- Reduce the public exposure while ambulatory when possible.

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
1) To describe the immune response to a booster dose of MenQuadfi® as measured by the serum bactericidal assay using human complement (hSBA) in toddlers aged 12-23 months, who had been primed with at least 1 dose of another MCV4 vaccine during infancy
2) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy
3) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with 2 doses of another MCV4 vaccine during infancy
4) To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 1 month after a booster dose of MenQuadfi® as measured by hSBA and rSBA in toddlers 12-23 months of age who had been primed with 1 dose of
	Immunogenicity
	1) hSBA antibody titers ≥ 1:8 (seroprotection) against meningococcal serogroups A, C, W and Y at D31 (+14 days) after booster vaccination with MenQuadfi®
	2) At Day (D)01 (baseline) before vaccination and at D31 [+14 days] after the administration of a booster dose of MenQuadfi® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by hSBA:
	• Antibody titers against meningococcal serogroups A, C, W, and Y
	• Antibody titers ≥ 1:4 and ≥ 1:8
	• ≥ 4-fold rise from pre-vaccination to post-vaccination
	• Vaccine seroresponse, defined as follows:
	  • For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16
	  • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer
	At Day (D)01 (baseline) before vaccination and at D31 [+14 days] after the administration of a booster dose of MenQuadfi® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by rSBA:
	• Antibody titers against meningococcal serogroups A, C, W, and Y
	• Antibody titers ≥ 1:8 and ≥ 1:128
	• ≥ 4-fold rise from pre-vaccination to post-vaccination
	• Vaccine seroresponse defined as follows:

Objectives	Endpoints
another MCV4 vaccine during infancy 5) To describe the antibody responses to tetanus toxoid before and 1 month after a booster dose of MenQuadfi® in toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy	• For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32 • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer 3) Same endpoints as described for endpoint #2 4) Same endpoints as described for endpoint #2 5) Antibody concentrations against tetanus toxoid at D01 (baseline) and at D31 (+14 days) after the administration of a booster dose of MenQuadfi®
Safety • To describe the safety profile of a booster dose of MenQuadfi® administered to toddlers 12-23 months of age who had been primed with at least 1 dose of another MCV4 vaccine during infancy	***Safety*** • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination. • Presence of solicited (pre-listed in the participant's diary card [DC] and case report form [CRF]) injection site reactions up to 7 days after vaccination. • Presence of solicited systemic reactions (pre-listed in the participant's DC and CRF) up to 7 days after vaccination. • Presence of unsolicited AEs up to 30 days after vaccination. • Presence of SAEs [including AESIs], throughout the trial from Visit 1 to 30 days after study vaccination. 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 descriptive, Phase IV, open-label, single-arm, un-controlled, multi-center study to describe the immunogenicity and safety of a single dose of the MenACYW conjugate vaccine administrated as a booster vaccine in healthy toddlers 12 – 23 months of age who had been primed before study participation with at least 1 dose of another quadrivalent meningococcal conjugate vaccine, ie, Nimenrix® (MCV4-TT) or Menveo® (MCV4-CRM), in infancy.

The eligible participant population for this booster vaccine administration will be recruited in Argentina from the general population who have received at least one of the 2 infant doses of quadrivalent meningococcal conjugate vaccine (Nimenrix® or Menveo®) recommended at 3-months or at 5-months of age.

All participants will receive a single booster dose of the MenACYW conjugate vaccine at Visit 1 on Day (D)01.

All participants will provide a 5 mL blood sample for immunogenicity assessments at D01, pre-vaccination (baseline) and 1-month post booster vaccination at D31 (+14 days).

Solicited AE information will be collected for 7 days after booster vaccination; 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 from D01 to D31 (+14 days) after study vaccination.

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Open-label, single-group, multi-center
Phase	IV
Control method	Un-controlled
Study population	Healthy toddlers aged 12 months to 23 months
Level and method of blinding	Open-label
Study intervention assignment method	No randomization
Number of participants	A total of approximately 180 participants (minimum of 30 evaluable participants from the low - enrolling of the 2 priming vaccines) are expected to be enrolled with the aim to obtain a total of 150 evaluable participants.
Intervention groups	All eligible participants (12 – 23-month-old toddlers who had received at least one of two priming doses of either Nimenrix® or Menveo® vaccine during infancy as part of their recommended immunization, before 12 months of age) will be assigned in an open-label design to receive a single booster dose of the MenACYW conjugate vaccine with an interval of at least 2 months after the last vaccination with Nimenrix® or Menveo®, as an intramuscular (IM) injection at D01.
Total duration of study participation	The duration of each participation will be approximately 1 month for each participant
Countries	Argentina
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 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 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 first marketing authorization for MenACYW conjugate vaccine was obtained in the US on 23 April 2020 (international birth date) and is currently licensed in more than 40 countries including the EU, under centralized procedure. 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 Argentina, with a single injection. Studies are ongoing to support the extension of indication from 6 weeks of age.

In the private vaccination clinics and NIP, MenACWY vaccination is included in the immunization calendar with a 2+1 schedule (at 3-, 5-, and 15-months) and a single dose at 11 years of age.

In Argentina, Menveo® and Nimenrix® are approved for use from 2-months of age and 6-weeks of age, respectively, and therefore can be used for the MenACWY vaccination schedule at 3-, 5-, and 15-18 months of age. While clinical studies are currently ongoing at Sanofi Pasteur to extend the indication of MenQuadfi® from 6 weeks of age, the current approval is for use in individuals 12 months of age and older. In this context, it is interesting to generate evidence that the MenACYW conjugate vaccine can be used as a booster dose in toddlers primed with Menveo® or Nimenrix®.

Mixing vaccines or vaccine interchangeability is when similar vaccines from different manufacturers authorized with the same indications are used for a vaccination series to complete a vaccination course (13). This can be in circumstances such as vaccine shortages, or when the details of initial vaccination are not known.

Different MenACWY vaccines are licensed, and even if it is preferable to use the same brand of MenACWY vaccine when giving subsequent doses, especially for completing a primary vaccination course for young children, any of the licensed quadrivalent meningococcal vaccine may be used regardless of which meningococcal vaccine was used for initial vaccination, according to the US recommendations of the Advisory Committee on Immunization Practices (ACIP) (14), or the Meningococcal vaccines – FAQ | NCIRS Fact sheet issued by the Australian National Centre for Immunization Research and Surveillance (15), or the Meningococcal vaccine: Canadian Immunization Guide (13).

It should be noted that current vaccines offering protection from meningococcal serogroup B disease are not interchangeable as these vaccines contain different antigens, and the same vaccine product is required for all priming and booster doses (13).

4.3 JUSTIFICATION FOR DOSE

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

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.

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

5.1 INCLUSION CRITERIA

Participants are eligible for the study only if all of the following criteria are met:

Age

I01: Aged 12 to 23 months on the day of inclusion[a]

Type Of Participant And Disease Characteristics

I02: Participants who are healthy as determined by medical evaluation including medical history, physical examination, and judgment of the Investigator

I03: Received at least one priming dose of licensed Nimenrix® or Menveo® vaccine during infancy before 12 months of age with an interval of at least 2 months between the last vaccination with Nimenrix® or Menveo® and the MenQuadfi® booster dose

Informed Consent

I04: 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

Other Inclusions

I05: Participant and parent/legally acceptable representative(s) are able to attend all scheduled visits and to comply with all study procedures

I06: Covered by health insurance, if required by local regulations

5.2 EXCLUSION CRITERIA

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

[a] "12 to 23 months" means from the day of the 12th month after birth to the day before the 24th month after birth

Medical Conditions

E01: 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)

E02: History of meningococcal infection, confirmed either clinically, serologically, or microbiologically

E03: At high risk for meningococcal infection 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)

E04: Personal history of Guillain-Barré syndrome

E05: Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine

E06: 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[b]

E07: Laboratory-confirmed thrombocytopenia, or known suspected thrombocytopenia, as reported by the parent/legally acceptable representative, contraindicating intramuscular injection

E08: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular injection

E09: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[c]

E10: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

[b] The components of study intervention are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

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

Prior/Concomitant Therapy

E11: Receipt of any vaccine (including COVID-19 vaccines) in the 4 weeks preceding the study intervention administration or planned receipt of any vaccine (including COVID-19 vaccines) in the 4 weeks following the study intervention administration except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after the study intervention. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

E12: Previous vaccination with a Meningococcal C vaccine or Meningococcal B (MenB) vaccine

E13: Receipt of immunoglobulins, blood or blood-derived products in the past 3 months

E14: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

Prior/Concurrent Clinical Study Experience

E15: Participation at the time of study enrollment (or in the 4 weeks preceding the study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other Exclusions

E16: Participant is in an emergency setting, or hospitalized involuntarily

E17: 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 should contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.3 LIFESTYLE CONSIDERATIONS

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study intervention. Screening information is recorded in the source documents.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened when the condition excluding them from participation is resolved (eg, fever, antibiotics received within 72 hours, etc).

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT / ADMINISTRATION OF STUDY INTERVENTION]

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 10.3: Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTION(S) 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(S) ADMINISTERED

Study interventions are described in Table 6.1.

Table 6.1: Study Intervention(s) Administered

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 Form	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(s)	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(s) or Alias(es)	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, AND ACCOUNTABILITY

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

It will be administered intramuscularly in the deltoid muscle of the upper arm according to country-specific recommendations.

The site of injection should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needles will be disposed of in accordance with currently established guidelines.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content, and extraneous particulate matter and/or discoloration, whenever solution and container permit. If any of these conditions exist, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor. The rubber stopper should not be removed from any of the vaccine vials.

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 will be provided to the study personnel.

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 an open-label study.

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 noncompliance 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

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 10.3: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

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 RMO 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

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.

Three standard categories of reportable medications are defined:

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

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

- 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 within 14 days pre or post each trial vaccination, including the day of the study vaccination visit and up to the last blood draw.

- Any vaccine other than study vaccines (vaccines non-described in the Protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study vaccination visit and up to the last blood draw.
- 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, 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 3: systemic (oral or injectable) antibiotics, received within 72 hours preceding each visit for blood draw related to IMP assessment (meningococcal vaccines) and used to define the PPAS, as they may interfere with bioassays used for antibody testing when taken before a blood draw.

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

Reportable medications will be collected in the CRF until the end of the solicited and unsolicited follow-up period.

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).

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 Form of the CRF unless the medication(s) received belong(s) to the reportable medications list. Medications will be coded using the WHODrug dictionary.

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.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1 DISCONTINUATION OF STUDY INTERVENTION

Not applicable as there is only one vaccination.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the request of his/her parents/legally acceptable representatives, 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.
- The participant will be permanently discontinued from the study intervention and the study at that time. However, 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.
- If the participants' parents/ legally acceptable representatives withdraw consent for disclosure of future information, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent.
- If a participants' parents/ legally acceptable representatives withdraw consent, they 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. However, in specific situations, if judged necessary and according to the number of withdrawn participants, the sample size may be increased to maintain the statistical power or the minimum number of evaluable participants of the study. Participants' numbers will not be reassigned.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he/she fails to return for Visit 2 and if participants' parents/legally acceptable representatives are 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 if participants' parents/legally acceptable representatives cannot be contacted as planned in the SoA:

- The site must attempt to contact the participants' parents/legally acceptable representatives and reschedule the missed visit as soon as possible, counsel the participants' parents/legally acceptable representatives on the importance of maintaining the assigned visit schedule, and ascertain whether the participants' parents/legally acceptable representatives wish to and/or should let their child 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 participants' parents/legally acceptable representatives (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 participants' parents/legally acceptable representatives continue to be unreachable, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness.
- 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.
- Exceptional situations (eg, COVID-19) may prevent access to the clinical trial sites. In these situations, site visits may be replaced by home visits where blood draw, physical examination and safety assessments will be performed by home nurses.

Blood samples will be collected as described in the SoA table (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 5 mL (at Visit 1 [BL0001] and Visit 2 [BL0002]) in total. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Temporary contraindications for blood sampling

Should a participant receive oral or injectable antibiotic therapy within 3 days (72 hours) prior to a 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 will result in the sample collection falling outside of the appropriate timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

Guidance and information for the sample collection, preparation, storage, and shipment will be provided to the study personnel.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.3: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

8.1 EFFICACY AND IMMUNOGENICITY ASSESSMENTS

Planned timepoints for all immunogenicity assessments are provided in the SoA.

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 hSBA and rSBA. The results will be expressed as vaccine seroresponse, seroprotection, and GMTs.

Antibodies to Meningococcal Antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in a serum bactericidal assay utilizing human complement. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with human complement are added to the serum dilutions and allowed to incubate. After this incubation period, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight at 37°C with 5% 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.

The hSBA testing will be performed at Global Clinical Immunology (GCI), Swiftwater, Pennsylvania or at qualified contract laboratories for GCI.

Antibodies to Meningococcal Antigens (rSBA Method)

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

The rSBA testing will be performed at Vaccine Evaluation Unit, Public Health Laboratory, Manchester [redacted], United Kingdom.

Antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine as a carrier protein will be determined in toddlers 12 – 23 months of age who received meningococcal conjugate vaccine (ie, Nimenrix or Menveo), in infancy. The results will be expressed as percentage of participants with antibody concentrations to tetanus toxoid ≥ 0.01 international units (IU)/mL and ≥ 0.1 IU/mL, and geometric mean concentrations (GMCs).

Tetanus (diphtheria, tetanus, pertussis multiplexed electrochemiluminescent [DTP-ECL] assay)

Anti-tetanus antibodies will be measured by DTP-ECL assay, a multiplexed serological assay which allows for the simultaneous quantification of human antibodies to 6 specific antigens including diphtheria toxoid, tetanus toxoid, and 4 pertussis antigens: pertussis toxin, filamentous haemagglutinin, fimbriae and pertactin.

In this assay, each well of a 96-well microtiter plate is pre-coated in precise positions with the 6 different antigens in a multi-spot fashion. Following incubation with serum samples, antigen specific antibodies bind to the respective antigens. The captured antibodies are then detected using a sulfotag-conjugated anti-human immunoglobulin (Ig)G conjugate. Electrical stimulation of the conjugate in the presence of a chemiluminescent substrate results in the generation of a light signal from each specific spot that is captured by a camera in relative light units. The signal generated is directly proportional to the amount of antibodies present in the sample, which is quantified using software and based on an established reference standard sample curve. For this study, only tetanus results will be calculated.

The tetanus antibody testing will be performed at Global Clinical Immunology (GCI), Swiftwater, Pennsylvania or at qualified contract laboratories for GCI.

8.2 SAFETY ASSESSMENTS

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

Planned timepoints 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. Collected information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For each condition, the data collected will be limited to

- Diagnosis (this is preferable to reporting signs and symptoms)

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 and Visit 2, the investigator or a designee will perform a clinical or medically-driven physical examination. Information will be recorded in the source document.

8.2.3 Vital Signs

Oral, rectal, or axillary route (axillary preferred) pre-vaccination temperature using a certified standard digital thermometer will be systematically collected by the Investigator on the source document (including the route of measurement). Other types of thermometer (tympanic scan, temporal artery scan and infrared skin scan) must not be used.

8.2.4 Clinical Safety Laboratory Tests

Not applicable.

8.2.5 Pregnancy Testing

Not applicable.

8.2.6 Viremia/Vaccinemia

Not applicable.

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 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 AE and SAE 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 the day of vaccination until 7 days after vaccination (D01 to D08).

Solicited systemic reactions will be collected from the day of vaccination until 7 days after vaccination (D01 to D08).

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

Unsolicited Non-serious Adverse Events

Unsolicited non-serious adverse events will be collected from the day of vaccination until 30 days after vaccination (D01 to D31 [+ 14 days]).

The intensity grading scale for unsolicited non-serious adverse events 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 (+14 days) post study vaccination.

See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from D01 to D31 (+14 days) post study vaccination. However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the case report form (CRF) (eg, SAEs related to blood sampling).

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 AEs and SAEs

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants' parents/legally acceptable representatives for the recording of daily safety information. These diary cards 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' 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' parents / legally acceptable representatives on how to correctly use these tools.

At specified intervals, the investigator or a designee will interview the participants' parents / legally acceptable representatives to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the investigator or designee using a web-based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participants' 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 AEs of special interest (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 SAEs

- 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 Boards (IRB)/Independent Ethics Committees (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

Not applicable as the study does not include women of childbearing potential.

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) (16)
- Kawasaki disease (17) (18) (19)
- Guillain-Barré syndrome (20)
- Idiopathic thrombocytopenic purpura (ITP) (21)

These events have been listed as AESIs based on the feedback received from the EU 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.

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

Any unused part of the biological samples collected for this study (blood samples) are being retained in long-term storage (for up to 25 years after the end of the study) to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results. The biological samples will be securely stored at the Sponsor's laboratory.

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.

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new vaccines/medicines. Reuse of coded data and biological samples (leftover) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study intervention to the Sponsor or which is co-developing the study intervention with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participants, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of samples will not be included in the local informed consent form [ICF]). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover samples.

Data Protection – Processing of Coded Clinical Data

The study participants will be provided with all mandatory details of the data processing in Part 2 of the ICF. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of Leftover Samples for Future Research

Remaining leftover samples will be used only after the study ends, ie end of study as defined in the study protocol.

The study participants will be provided with all mandatory details of the use of their biological samples (leftover) in Part 2 of the ICF.

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study.

Any samples remaining at the end of the retention period will be destroyed. If a participant requests destruction of his/her 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 related coded data will be anonymized unless otherwise required by applicable laws.

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 hypotheses will be tested. The analyses will be descriptive.

Details on statistical methods are provided in Section 9.3.

9.2 ANALYSIS SETS

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Safety Analysis Set (SafAS)	Participants who have received the study vaccine. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of SafAS. Participants who received the study vaccine and had a valid post-vaccination serology result. Participants will be analyzed according to the intervention they received.
Per-protocol analysis set (PPAS)	Subset of FAS. Participants presenting with at least 1 of the following relevant protocol deviations will be excluded from the PPAS: • Participant did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria • Participant did not receive the study vaccine • Preparation and/or administration of vaccine was not done as per-protocol • Participant did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn Blood sampling 2 (BL0002) / Visit 2: Visit 1+ 30 day (+14 days)

Participant Analysis Set	Description
	• Participant's serology sample did not produce a valid test result (ie, results for all meningococcal antigens are missing) • Participant had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database • Participant received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine

9.3 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 described in this section. This section is a summary of the planned statistical analyses of all the endpoints.

9.3.1 General Considerations

Immunogenicity analyses will be performed on the PPAS and FAS. Safety analysis will be performed on the SafAS.

9.3.2 Immunogenicity Endpoints

Descriptive statistics will be provided for the hSBA and rSBA antibody titers against meningococcal serogroups (A, C, W, and Y) and for antibody concentrations against tetanus toxoid contained in MenQuadfi® as a carrier protein.

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

For immunogenicity data, assuming that log10 transformation of the titers / concentrations follows a normal distribution, first, the mean and 95% CIs will be calculated on log10 (titers / concentrations) using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, to compute GMTs / GMCs and their 95% CIs.

Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups and the antibody concentrations against tetanus toxoid contained in MenQuadfi®.

In summary, descriptive analyses on A, C, Y, and W serogroups on D01 and D31 after vaccination with MenACYW conjugate vaccine will include but not be limited to:

- hSBA and rSBA GMTs and 95% CI
- hSBA and rSBA titer distribution and RCDC
- Percentage of participants with hSBA titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of participants with rSBA titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Percentage of participants with hSBA and rSBA titer ≥4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of participants with hSBA and rSBA vaccine seroresponse rate and 95% CI

  hSBA vaccine seroresponse for serogroups A, C, Y, and W 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

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

In addition, descriptive analyses on anti-tetanus antibody concentrations will include but not be limited to:

- GMCs and 95% CI
- The percentage of participants with antibody concentrations to tetanus toxoid ≥ 0.01 international units (IU)/mL and ≥ 0.1 IU/mL and 95% CI

All immunogenicity analyses will be performed on the PPAS (evaluable participants) and presented overall and by priming vaccine.

9.3.3 Safety Endpoints

Safety

Safety analyses will be performed on the SafAS and presented overall and by priming vaccine. The main parameters for the safety endpoints will be described by 95% CIs using the Exact binomial method (Clopper-Pearson method).

9.3.4 Other Endpoints

Same statistical analyses will be applied as described above for the description of the other immunogenicity endpoints.

9.4 INTERIM ANALYSES

An interim report may be generated with hSBA analysis of all immunogenicity endpoints and safety endpoints depending on the timelines regarding the availability of the rSBA data. Final report will be generated with the analyses of rSBA immunogenicity endpoints.

This study will not include an early safety data review. No additional analyses are planned to be performed prior to the formal completion of the study.

9.5 SAMPLE SIZE DETERMINATION

There are no statistically powered hypotheses in this study thus no formal sample size computation. All analyses will be descriptive.

The sample size was set to approximatively 180 participants (minimum of 30 evaluable participants from the low - enrolling of the 2 priming vaccines) to have at least 150 evaluable participants assuming a drop-out rate of approximatively 15%.

In terms of immunogenicity for any of the 4 serogroups, considering a sample size of 150 evaluable subjects, the expected precision of the 95% CI using the Exact binomial method will be as follow:

Seroprotection rates (titer >= 1:8)	**Precision***
85%	13.77
90%	11.62
95%	8.96
100%	2.88

*Difference between the upper and lower bounds of the 95%CI

In terms of safety, the planned sample size will allow for identification of common AEs. One hundred and fifty evaluable subjects will allow with 95% probability, the detection of an AE occurring with a frequency of 2% or more, using the rule of threes.

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, ICF, Investigator's Brochure (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 participants' parents/legally acceptable representatives (and/or his/her designated healthcare professional, if so designated by the participants' parents/legally acceptable representatives) 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 participants' parents/legally acceptable representatives in a clinical study have the right to opt out of being notified by the investigator of such incidental findings. In the event that the participants' parents/legally acceptable representatives have 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 participants' parents/legally acceptable representatives have 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

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

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, including the risks and benefits, to the participants' parents / legally acceptable representatives and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).

- Parents / legally acceptable representatives must be informed that their child's participation is voluntary. Participants' parents / legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

- If new information becomes available that may be relevant to the participants' parents' / legally acceptable representatives' willingness to continue their child's participation in the study, this will be communicated to the participants' parents/legally acceptable representatives in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

- Participants' parents/legally acceptable representatives must be reconsented to the most current version of the ICF(s) during their participation in the study. Where participants are not in the study anymore, the Sponsor must define if those participants must or not re-consent or be informed of the revision (eg, if the processing of personal data is modified, if the Sponsor changes).

- A copy of the ICF(s) must be provided to the participant's parents / legally acceptable representatives.

The ICF will contain a separate section that addresses the use of remaining mandatory for research of participants' data and/or samples (remaining mandatory ones for optional research). Each option is subject to an independent consent and must be confirmed by ticking checkboxes in ICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of additional biological samples for storage and use for future research. The investigator or authorized designee will explain to each participant's parent/ legally acceptable representative the objectives of the exploratory research and why data and samples are important for future research. Participant's parent/ legally acceptable representative will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Rationale for Including Participants Unable to Give Consent

MEQ00086 is a study to be conducted to describe the immunogenicity and safety of the MenACYW conjugate vaccine when administered as a booster dose in healthy toddlers 12 – 23 months of age who had been primed during the first year of life with at least 1 dose of another licensed quadrivalent meningococcal conjugate vaccine, either Nimenrix® (MCV4-TT) or Menveo® (MCV4 - CRM).

Since these participants are unable to give their consent, written informed consent must be obtained from the parent 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/ 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 Procedures

Before the start of the study, the Investigator or sub-investigator will contact an appropriate pool of potential participants (independent of the Investigator and investigational team) and invite them to participate in the study. The site will ensure that any advertisements used to recruit participants (eg, letters, pamphlets, posters) are submitted to Sanofi Pasteur prior to submission to the IEC/IRB for approval.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.3: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data Protection

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 (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including investigators, nurses, experts, service providers, Ethics Committee members, etc.

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.

Protection of participant personal data

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' race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African-American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- 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 participants' parents/legally acceptable representatives must be informed that their child's personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participants' parents/legally acceptable representatives as described in the informed consent.

- The participants' parents/legally acceptable representatives must be informed that their child'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.

- Participants' parents/legally acceptable representatives must be informed that their child's study-related data will be used for the whole "product development program", ie, for this study as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.

- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).

- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.

- Personal data can be communicated to the following recipients:

  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to object to the processing, to request for access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees Structure

Participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study. The Sponsor's internal safety review committee, led by the PV representative and the RMO, will be responsible

for the review, assessment, and evaluation of safety data generated from this study. This committee is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

10.1.6 Dissemination of Clinical Study Data

Study Participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

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 https://vivli.org.

Individual participant data and supporting clinical documents are available for request at https://vivli.org. 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: https://vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs 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.
- Guidance on completion of CRFs will be provided in CRF Completion Instructions.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy including definition of study critical data items and processes (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 onsite 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).
- Records and documents, including signed ICFs, 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.
- The protocol will be signed by the RMO, and a Protocol Investigator Agreement Form (PIAF) will be signed by all investigators. The clinical study report will be signed by the RMO and the coordinating investigator. In case no coordinating investigator has been designated, it will be the responsibility of the RMO or designee(s) to identify the signatory investigator.

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, diary cards, medical and hospital records, screening logs, informed consent / assent forms, 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

10.1.9 Study and Site Start and Closure

Study personnel will be informed of which clinical supplies will be provided by the Sponsor or the site.

The study start date is considered the date of the first visit planned in the SoA of the first participant.

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:

For study termination:

- Discontinuation of further study intervention development
- Information on the study intervention leads to doubt as to the benefit/risk ratio
- For site termination:
- 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 (evaluated after a reasonable amount of time) of participants by the investigator
- 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 contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant 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: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.2.1 Definition of SAE

An SAE 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) that 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

- The term "Other medically important events" refers to events which do not meet any of the above seriousness criteria, but which are considered as serious based on investigator medical judgment.
- 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.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse, new-onset diabetes or autoimmune disease, or suspected transmission of any infectious agent via an authorized medicinal product.

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.

10.2.2 Definition of AE

AE 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 AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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 condition 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 AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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:

An adverse reaction (AR) is any noxious and unintended response to a study intervention related to any dose.

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs which occur within the first 30 minutes after vaccination.

Reactogenicity / Solicited Reactions:

The **reactogenicity** of a vaccine refers to the property of such vaccine to be able to produce common "expected" adverse reactions (either systemic or at the injection site) and its associated signs and symptoms.

A solicited reaction is an “expected” adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF ([eg, injection site pain or headache occurring between the day of vaccination and the next 7 days]).

By definition, solicited reactions are considered as being related to the corresponding IMP administered.

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

Injection / Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site of the IMP. Injection/administration site reactions are commonly inflammatory reactions.

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

Note: « Administration site reaction » term is only to be used for vaccines that are not intended to be administered by injection.

Systemic AR:

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).

Solicited systemic reactions are systemic AEs observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. Solicited systemic reactions occurring during the specified collection period are always considered related to the IMP even if there is evidence of alternative etiology.

Unsolicited AE/AR:

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 an IMP.

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

All unsolicited AEs occurring at and around the IMP injection/administration site are to be considered by default as related to the IMP administered at that site and are therefore referred as unsolicited injection/administration site ARs.

All unsolicited AEs which are not at and around the IMP injection/administration site, are referred as systemic unsolicited AE. For each unsolicited systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs.

Adverse Event of Special Interest (AESI):

An adverse event of special interest (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.

10.2.3 Recording and Follow-Up of AE and/or SAE

AE and SAE 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.
- 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 IMP (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 (except for injection site reactions which will be related by default). 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 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.

Follow-up of AEs and SAEs

- 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 submitted documents.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Serious adverse events likely to be related to the study intervention, 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 SAEs

SAE 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).

SAE Reporting to the Sponsor via Paper CRF

- The SAE paper CRF can be sent to the Sponsor by one of the following means:
  - By fax, to the following number: (570) 957 - 2782
  - In PDF format to the following email address, using a method of transmission that includes password protection: PV.outsourcing@sanofipasteur.com
  - 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

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 Sponsor contact, as needed. The toll-free contact information for the Call Center will be provided separately.

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.

In case of emergency code-breaking, the investigator is required to follow the code-breaking procedures described in Section 6.3.2.

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 "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:** CRF and DC: Minor reaction when injection site is touched **Grade 2:** CRF and DC: 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 DC: 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

* 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 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 (≥ 100.4°F)	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 **or** ≥ 100.4°F to ≤ 101.3°F	**Grade 1:** CRF and DC: 1 episode per 24 hours	**Grade 1:** CRF and DC: < 1 hour	**Grade 1:** CRF and DC: Sleepier than usual or less interested in surroundings	**Grade 1:** CRF and DC: Eating less than normal	**Grade 1:** CRF and DC: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	**Grade 2:** CRF and DC: 2–5 episodes per 24 hours	**Grade 2:** CRF and DC: 1–3 hours	**Grade 2:** CRF and DC: Not interested in surroundings or did not wake up for a feed / meal	**Grade 2:** CRF and DC: Missed 1 or 2 feeds / meals completely	**Grade 2:** CRF and DC: Requiring increased attention
	Grade 3: > 39.5°C **or** > 103.1°F	**Grade 3** CRF: ≥ 6 episodes per 24 hours or requiring parenteral hydration DC: at least 6 episodes per 24 hours or requiring intravenous hydration (fluids administered in the arm or leg)	**Grade 3:** CRF and DC: > 3 hours	**Grade 3:** CRF and DC: Sleeping most of the time or difficult to wake up	**Grade 3:** CRF and DC: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	**Grade 3:** CRF: Inconsolable DC: Inconsolable (cannot be comforted)

* 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 parents / legally acceptable representatives are to measure body temperature once per day, preferably always at the same time, and using the same standard unit of the considered country (Celsius or Fahrenheit) consistently. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is axillary.

10.2.5.1.2 Serious and Non-serious 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, including SAEs, 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.
  - Diary card: No interference with activity.
- 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.
  - Diary card: Some interference with activity.
- 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.
  - Diary card: Significant; prevents daily activity.

10.3 APPENDIX: MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical study site.

Contingency procedures are suggested below and in Section 5.5, Section 6.4, Section 8, and Section 10.1.3 for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect study integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement must be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site is unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical study should be proposed, and enrollment administration of study intervention, and blood sampling may be temporarily delayed/halted.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible visit windows may be extended for assessment of safety data that cannot be obtained remotely.

Contingencies implemented due to emergency will be documented.

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
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sampling
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
D	day
DC	diary card
DNA	deoxyribonucleic acid
EU	European Union
FAS	full analysis set
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
GPV	Global Pharmacovigilance
hSBA	serum bactericidal assay using human complement
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IM	intramuscular
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IRB	Institutional Review Boards
MCV4	quadrivalent meningococcal conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NIMP	non-investigational medicinal product
PIAF	Protocol Investigator Agreement Form

PPAS	per-protocol analysis set
PV	pharmacovigilance
RCDC	reverse cumulative distribution curve
RMO	Responsible Medical Officer
rSBA	serum bactericidal antibody assay using baby rabbit complemen
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SoA	schedule of activities
SUSARs	suspected unexpected serious adverse reactions
TBD	to be determined
TC	telephone call
TT	tetanus toxoid
US	United States

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12 SPONSOR SIGNATURE PAGE

Signature Page for VV-CLIN-0629982 v2.0
menquadtt-meq00086-protocol

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]