NCT06284915

Clinical Study Protocol

Protocol Title:

A parallel-group, prevention, Phase III, modified double-blind, 2-arm, study to investigate the immunogenicity and describe the safety of a quadrivalent meningococcal conjugate vaccine (MenACYW conjugate vaccine) compared with Nimenrix® when administered in a 1+1 schedule in healthy infants and toddlers at 6 and 12 months of age

Study Code: MEQ00089

Amendment Number: 2.0

Compound: MenACYW conjugate vaccine (MenQuadfi®)

Brief Title:

Study on immunogenicity and safety of a meningococcal ACYW conjugate vaccine in healthy infants and toddlers

Study Phase: Phase III

Sponsor Name and Legal Registered Address:

Sanofi Winthrop Industrie
14 Espace Henry Vallée, 69007 Lyon, France

Manufacturer:

Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Regulatory Agency Identifier Number(s):

Registry	ID
EU Trial Number	2023-508177-85
WHO UTN	U1111-1280-6981
PIP Number	EMEA-001930-PIP01-16
EU MAA Number	EU/1/20/1483

Protocol Version Number: 7.0

Approval Date: 08 April 2025

Medical Monitor(s) Name and Function:

Responsible medical officer (RMO): [redacted], MD (Global Medical Product Leader)

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

Document History

Previous Version(s)*	Date	Comments
1.0	09 May 2023	Version not approved by the IEC/IRB
2.0	23 August 2023	Version not approved by the IEC/IRB
3.0	06 September 2023	Version not approved by the IEC/IRB
4.0	12 September 2023	Version not approved by the IEC/IRB
5.0	17 January 2024	First version used in the study
6.0	27 August 2024	Amendment 1.0

IEC: Independent Ethics Committee; IRB: Institutional Review Board

* Versions in bold font have been approved by the IEC(s) / IRB(s) and used in the study.

Amendment 2 (08 April 2025)

This amendment (amendment 2) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Sanofi is amending the MEQ00089 protocol to add seroresponse post-booster dose as a coprimary endpoint upon which non-inferiority of MenACYW conjugate vaccine vs Nimenrix® will be assessed. As Study MEQ00089 is being conducted, in part, to infer the efficacy of MenACYW conjugate vaccine through an evaluation of its immunogenicity, the primary endpoint should include a surrogate measure with a demonstrated ability to predict clinical benefit. Accordingly, seroresponse is being added as a coprimary endpoint to better understand the performance of MenACYW conjugate vaccine post-booster beyond what non-inferiority based solely on GMTs can provide.

Table of Contents

Document History **3**

Table of Contents **4**

List of Tables **8**

List of Figures **9**

Abbreviations **10**

1 Protocol Summary **12**

1.1 Synopsis 12

1.2 Schema 24

1.3 Schedule of Activities (SoA) 25

2 Introduction **28**

2.1 Study Rationale 28

2.2 Background 30

2.3 Benefit/Risk Assessment 31

2.3.1 Risks from Study Participation 31

2.3.2 Benefits from Study Participation 34

2.3.3 COVID-19 Risk Assessment 34

2.3.4 Overall Benefit-Risk Conclusion 34

3 Objectives and Endpoints **35**

4 Study Design **40**

4.1 Overall Design 40

4.2 Scientific Rationale for Study Design 41

4.3 Justification for Dose 41

4.4 End of Study Definition 42

5 Study Population **43**

5.1 Inclusion Criteria 43

5.2 Exclusion Criteria 43

5.3 Lifestyle Considerations 45

5.4 Screen Failures 45

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention....45

6 Study Intervention(s) and Concomitant Therapy....46

6.1 Study Intervention(s) Administered....46

6.2 Preparation, Handling, Storage, and Accountability....48

6.3 Assignment to Study Intervention....49

6.4 Blinding....50

6.5 Study Intervention Compliance....51

6.6 Dose Modification....51

6.7 Continued Access to Study Intervention After the End of the Study....51

6.8 Treatment of Overdose....51

6.9 Prior and Concomitant Therapy....51

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal....54

7.1 Discontinuation of Study Intervention....54
7.1.1 Temporary Contraindications....54
7.1.2 Definitive Contraindications....54
7.1.3 Other Reasons....55

7.2 Participant Discontinuation/Withdrawal from the Study....55

7.3 Lost to Follow-up....56

8 Study Assessments and Procedures....57

8.1 Administrative and General Procedures....57
8.1.1 Medical History....57
8.1.2 Sample Collection....57

8.2 Efficacy and Immunogenicity Assessments....58
8.2.1 Efficacy Assessments....58
8.2.2 Immunogenicity Assessments....58

8.3 Safety Assessments....59
8.3.1 Physical Examinations....59
8.3.2 Vital Signs....59

8.4 Adverse Events (AEs), Serious Adverse Events, and Other Safety Reporting....59
8.4.1 Time Period and Frequency for Collecting AE and SAE Information....60
8.4.2 Method of Detecting AEs and SAEs....61
8.4.3 Follow-up of AEs and SAEs....61
8.4.4 Regulatory Reporting Requirements for SAEs and Other Safety Reporting....61
8.4.5 Pregnancy....62

8.4.6 Adverse Events of Special Interest 62
8.4.7 Medication Errors, Misuses or Abuses of Medicinal Product 62
8.5 Pharmacokinetics 62
8.6 Pharmacodynamics 62
8.7 Genetics 63
8.8 Biomarkers 63
8.9 Immunogenicity Assessments 63
8.10 Medical Resource Utilization and Health Economics 63
8.11 Leftover Biological Samples 63
8.12 Use of Biological Samples And Data For Future Research 63
9 Statistical Considerations 65
9.1 Statistical Hypotheses 66
9.1.1 Multiplicity Adjustment 67
9.2 Analysis Sets 67
9.2.1 Full Analysis Set (FAS) 68
9.2.2 Per-Protocol Analysis Set (PPAS) 68
9.2.2.1 hSBA PPAS for Dose 1 (priming dose) 68
9.2.2.2 hSBA PPAS2 for Dose 2 (booster dose) 69
9.2.2.3 rSBA PPAS1 for Dose 1 (priming dose) 69
9.2.2.4 rSBA PPAS2 for Dose 2 (booster dose) 69
9.2.2.5 Safety Analysis Set 70
9.2.2.5.1 Overall Safety Analysis Set for Any Dose 70
9.2.2.5.2 Safety Analysis Set for Vaccination at 6 Months of Age 70
9.2.2.5.3 Safety Analysis Set for Vaccination at 12 Months of Age 70
9.3 Statistical Analyses 71
9.3.1 General Considerations 71
9.3.2 Coprimary Endpoint Analysis 71
9.3.3 Secondary Endpoints Analysis 71
9.3.4 Exploratory Endpoints Analysis 73
9.3.5 Safety Analysis 74
9.3.6 Other Analysis 74
9.4 Interim Analyses 74
9.5 Sample Size Determination 74
10 Supporting Documentation and Operational Considerations 76
10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations 76
10.1.1 Regulatory and Ethical Considerations 76
10.1.2 Financial Disclosure 78

10.1.3 Informed Consent Process 78
10.1.4 Data Protection 79
10.1.5 Committees Structure 82
10.1.6 Dissemination of Clinical Study Data and Results 83
10.1.7 Data Quality Assurance 83
10.1.8 Source Documents 84
10.1.9 Study and Site Start and Closure 85
10.1.10 Publication Policy 85
10.2 Appendix: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 86
10.2.1 Definition of AE 86
10.2.2 Definition of SAE 88
10.2.3 Recording and Follow-Up of AE and/or SAE 90
10.2.4 Reporting of SAEs 92
10.2.5 Assessment of Intensity 93
10.2.5.1 Tables for Clinical Abnormalities 93
10.2.5.1.1 Solicited AR Intensity Grading Scale 93
10.2.5.2 Serious and Non-serious Unsolicited AE Intensity Grading Scale 95
10.3 Appendix: Medication Errors, Misuses or Abuses of Medicinal Product 95
10.4 Appendix: Country-specific/Region Requirements 96
10.4.1 European Union 96
10.4.1.1 Safety Reporting to the Agency 96
10.5 Appendix: Contingency Measures for a Regional or National Emergency That is Declared by a Governmental Agency 96
10.6 Appendix: Collection, Storage, And Future Use of Data And Human Biological Samples 97
10.6.1 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of Human Biological Samples (Article 7.1h) of EU Regulation 536/2014 97
10.6.2 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of (Personal) Data (Article 7.1d) of EU Regulation 536/2014 97
10.7 Appendix: Risk-based Approach 97
10.8 Appendix: Protocol Amendment History 97
11 References 98
12 Sponsor Signature Page 100

List of Tables

Table 1.1: Schedule of activities 25
Table 2.1: Identified and Potential risks of clinical significance and risk mitigation / management.....31
Table 3.1: Objectives and endpoints 35
Table 4.1: Overall design 40
Table 6.1: Study Intervention(s) Administered 46
Table 6.2: Study Arm(s) 48
Table 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales – Infants and toddlers aged < 24 months 93
Table 10.2: Solicited systemic reactions: terminology, definitions, and intensity scales – Infants and toddlers aged < 24 months 94

List of Figures

Figure 1: Graphical study design.....24

Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
AxMP	auxiliary medicinal product
CI	confidence interval
CRF	case report form
EU	European Union
FAS	full analysis set
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	geometric mean titers
hSBA	serum bactericidal assays using human complement
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	inteactive response technology
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MCC	monovalent meningococcal C
MCV4	quadrivalent meningococcal ACWY
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	non-investigational medicinal product
PIAF	Protocol Investigator Agreement Form
PPAS	per-protocol analysis set
PSPV	Patient Safety and Pharmacovigilance

PV	pharmacovigilance
QTL	quality tolerance limit
RMO	Responsible Medical Officer
rSBA	serum bactericidal assays using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TT	tetanus toxoid
US	United States

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:

A parallel-group, prevention, Phase III, modified double-blind, 2-arm, study to investigate the immunogenicity and describe the safety of a quadrivalent meningococcal conjugate vaccine (MenACYW conjugate vaccine) compared with Nimenrix® when administered in a 1+1 schedule in healthy infants and toddlers at 6 and 12 months of age

Brief Title:

Study on immunogenicity and safety of a meningococcal ACYW conjugate vaccine in healthy infants and toddlers

Regulatory Agency Identifier Number(s):

Registry	**ID**
EU Trial Number	2023-508177-85
WHO UTN	U1111-1280-6981
PIP Number	EMEA-001930-PIP01-16
EU MAA Number	EU/1/20/1483

Rationale:

The meningococcal ACYW conjugate vaccine also identified as Meningococcal Polysaccharide [Serogroups A, C, Y, and W] Tetanus Toxoid (TT) Conjugate Vaccine, MenACYW conjugate vaccine, or MenACYW-TT, or MenQuadfi® is currently licensed in Europe and other countries for active immunization of individuals from the age of 12 months and older with a single dose. An extension of the indication of MenACYW conjugate vaccine in the European Union (EU) down to 6 weeks of age has been planned and will be supported by clinical safety and immunogenicity data following use of the vaccine from 6 weeks of age with a 3-dose series (ie, a 2+1 vaccination schedule) administered at 2, 4 and 12 months of age in infants/toddlers and conducted with Nimenrix® as a comparator (MET58).

Study MEQ00089 will be conducted to support a 2-dose series (ie, a 1+1 vaccination schedule) in the EU for immunization of individuals from 6 months of age. It is designed to evaluate the non-inferiority of the immunological response of MenACYW conjugate vaccine against the EU - approved comparator vaccine Nimenrix® after completion of the 2-dose series (1+1 vaccination schedule), with the first (priming) dose being given at 6-7 months of age to MenACWY- naïve healthy infants and the second (booster) dose given at 12-13 months of age. This study will also describe additional immunogenicity parameters and safety of MenACYW conjugate vaccine versus Nimenrix® in the same population of participants. A comparable study (MET61) in the same age group conducted in the United States (US) with Menveo® as the comparator also provides additional data to support the 1+1 immunization schedule starting at 6-7 months of age.

Objectives, Endpoints:

Objectives	Endpoints
Coprimary	
Immunogenicity 1. To demonstrate non-inferiority of the antibody response in terms of geometric mean titers (GMTs) against meningococcal serogroups A, C, W, and Y, following the administration of a 2-dose series (1+1) of MenACYW conjugate vaccine compared to a 2-dose series (1+1) of Nimenrix®, when each vaccine is administered to infants (Dose 1) at 6-7 months of age and toddlers (Dose 2) at 12-13 months of age 2. To demonstrate non-inferiority of the antibody response in terms of vaccine seroresponse against meningococcal serogroups A, C, W, and Y, following the administration of a 2-dose series (1+1) of MenACYW conjugate vaccine compared to a 2-dose series (1+1) of Nimenrix®, when each vaccine is administered to infants (Dose 1) at 6-7 months of age and toddlers (Dose 2) at 12-13 months of age	***Immunogenicity*** 1. Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assays using human complement (hSBA) at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] with MenACYW conjugate vaccine or Nimenrix®, at 12-13 months of age 2. Vaccine seroresponse against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assays using human complement (hSBA) at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] with MenACYW conjugate vaccine or Nimenrix®, at 12-13 months of age Vaccine seroresponse is defined as follows: • For a participant with a pre-vaccination (pre-Dose 1) titer < 1:8, a post-vaccination (post-Dose 2) titer ≥ 1:16 • For a participant with a pre-vaccination (pre-Dose 1) titer ≥ 1:8, a post-vaccination (post-Dose 2) titer at least 4-fold greater than the pre-vaccination (pre-Dose 1) titer
Secondary	
Immunogenicity 1. To compare the antibody response in terms of seroprotection as measured by hSBA against meningococcal serogroups A, C, W and Y, 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine versus Dose 1 (priming dose) of Nimenrix® in infants 6-7 months of age	***Immunogenicity*** 1. Antibody titers ≥ 1:8, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®

Objectives	Endpoints

2. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at Day (D)01 (baseline) before vaccination and 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants 6-7 months of age	2. At Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® 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 in antibody titer from pre-vaccination to post-vaccination
	• Vaccine seroresponse, defined as follows:
	  • For a participant with a pre-vaccination (pre-Dose 1) titer < 1:8, a post-vaccination (post-Dose 1) titer ≥ 1:16
	  • For a participant with a pre-vaccination (pre-Dose 1) titer ≥ 1:8, a post-vaccination (post-Dose 1) titer at least 4-fold greater than the pre-vaccination (pre-Dose 1) titer

3. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, before and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers 12-13 months of age	3. Same endpoints as described in secondary endpoint #2 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
4. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before Dose 1 (priming dose) as infants 6 – 7 months of age and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® as toddlers at 12-13 months of age	4. Same endpoints (except vaccine seroresponse) as described in secondary endpoint #2 at Visit 1 before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
5. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before vaccination and at 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants at 6-7 months of age	5. At Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by rSBA:

Objectives	Endpoints

	• Antibody titers against meningococcal serogroups A, C, W, and Y
	• Antibody titers ≥ 1:8 and ≥ 1:128
	• ≥ 4-fold rise in antibody titer 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 than the pre-vaccination titer

6. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, before and at 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers at 12-13 months of age	6. Same endpoints as described in secondary endpoint #5 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
7. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before Dose 1 (priming dose) as infants 6 – 7 months of age and at 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® as toddlers at 12-13 months of age *rSBA testing will be performed in a subset of participants, the first 100 participants enrolled into each study group.	7. Same endpoints as described in secondary endpoint #5 at Visit 1 (D0) before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
Safety 1. To describe the safety profile of MenACYW conjugate vaccine and Nimenrix® after Dose 1 (priming dose) administered to infants at 6-7 months of age and after Dose 2 (booster dose) administered at 12-13 months of age	***Safety*** 1. Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination. 2. Presence of solicited (pre-listed in the participant's diary card [DC] and case

Objectives	Endpoints
	report form [CRF]) injection site reactions up to 7 days after each vaccination. 3. Presence of solicited systemic reactions (pre-listed in the participant's DC and CRF) up to 7 days after each vaccination. 4. Presence of unsolicited AEs up to 30 days after each vaccination. 5. Presence of serious adverse events (SAEs) [including AESIs], throughout the trial. 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

Overall Design:

Type of design	Randomized, parallel-group, 2-arm, active-controlled, multi-center
Phase	III
Control method	Active-controlled (control = EU licensed quadrivalent meningococcal polysaccharide conjugate vaccine Nimenrix®)
Study population	Healthy infants and toddlers aged 6 to 7 months of age at inclusion (at Dose 1) to 12-13 months of age (at Dose 2)
Countries	Several countries in the European Union
Level and method of blinding	Modified double-blind
Investigational intervention assignment method	Randomization

Inclusion/Exclusion Criteria

Inclusion criteria

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

Age

I01: Aged 6 to 7 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

Informed Consent

I03: 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

I04: Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

I05: Covered by health insurance, if required by local regulations

[a] "6 to7 months" means from the day of the 6th month after birth to the day before the 8th month after birth

Exclusion criteria

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

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(s) used in the study or to a product containing any of the same substances[b]

E07: Laboratory-confirmed thrombocytopenia, or 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(s) 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 and Meningococcal B vaccines) in the 4 weeks preceding the first and second study intervention administration or planned receipt of any vaccine (including COVID-19 and Meningococcal B vaccines) in the 4 weeks following any study intervention administration except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after the study interventions. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines

E12: Previous vaccination against meningococcal A, C, W, or Y disease with either the trial vaccine or another vaccine (i.e., mono- or quadrivalent meningococcal conjugate vaccine) containing serogroups A, C, W, or Y

E13: Receipt of immune globulins, 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 first 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

Brief Summary:

The purpose of this study is to evaluate the non-inferiority of the immune response of MenACYW conjugate vaccine to Nimenrix® following a 1+1 administration schedule (2-dose series) in healthy Meningococcal A, C, W, and Y- naïve infants at enrollment. Participants can be exposed to Meningococcal B (MenB) vaccine.

The first (priming) dose will be administrated at 6 to 7 months of age and the second (booster) dose at 12 to 13 months of age. This study will also describe the immunogenicity and safety of MenACYW conjugate vaccine and Nimenrix® and will be conducted in several countries in the European Union.

Study details include the following:

- Eligible participants will be randomized to 2 groups in a 1:1 ratio:
  - Group 1: MenACYW conjugate vaccine (approximately n=420)
  - Group 2: Nimenrix® (approximately n=420)
- The study duration will be approximately 7 to 8.5 months (at least 7 months per participant).

- The treatment duration: participants will receive a priming dose (Dose 1) of either MenACYW conjugate vaccine or Nimenrix® at 6-7 months of age and a booster dose (Dose 2) at 12-13 months of age.
- All participants will provide a 3 mL blood sample for immunogenicity assessments at each of the following visits:
  BL0001 at Visit 1: D01, pre-vaccination (baseline / pre-Dose 1 / pre-priming)

  BL0002 at Visit 2: 30 days [+14 days] after Dose 1 (priming vaccination)

  BL0003 at Visit 3: at 6 months after Visit 1 [+14 days] pre-Dose 2 /pre-booster vaccination

  BL0004 at Visit 4: 30 days [+14 days] after Dose 2 (booster vaccination).
- Presence of any unsolicited systemic AEs reported in the 30 minutes after each vaccination will be collected.

  Solicited AE information will be collected for 7 days after primary (Dose 1) and booster (Dose 2) vaccinations;

  Unsolicited AE information will be collected up to 30 days after each vaccination, and

  SAE information (including AESIs) will be collected throughout the study.

Number of Participants:

A total of approximately 840 participants (420 per group) is expected to be randomized with the aim to obtain a total of 672 (336 per group) evaluable participants.

Study Arms and Duration:

Eligible participants (infants 6-7 months of age) will be randomized to 2 parallel groups in a 1:1 ratio to receive a single intramuscular (IM) injection of either MenACYW conjugate vaccine (Group 1) or Nimenrix® (Group 2) at Visit 1 (D01) (Dose 1 / priming dose) and at Visit 3 [+14 days] (Dose 2 / booster dose) at 12-13 months of age.

The duration of participation will be approximately 7 to 8.5 months (at least 7 months) for each participant.

Study intervention(s):

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:
  - *Neisseria meningitidis* group A polysaccharide* 10 µg
  - *Neisseria meningitidis* group C polysaccharide* 10 µg
  - *Neisseria meningitidis* group W polysaccharide* 10 µg
  - *Neisseria meningitidis* group Y polysaccharide* 10 µg

* conjugated to 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

Investigational medicinal product: **Nimenrix®**: Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)

- Form: white powder or cake in a single-dose glass vial and a clear and colorless solvent in a pre-filled syringe
- Composition: After reconstitution, each 0.5 mL dose of Nimenrix® contains:
  - *Neisseria meningitidis* group A polysaccharide[‡] 5 µg
  - *Neisseria meningitidis* group C polysaccharide[‡] 5 µg
  - *Neisseria meningitidis* group W-135 polysaccharide[‡] 5 µg
  - *Neisseria meningitidis* group Y polysaccharide[‡] 5 µg

[‡]conjugated to tetanus toxoid protein carrier 44 µg

The vaccine also contains the excipients: sucrose, trometamol, sodium chloride, water for injections

- Route of administration: IM injection

Statistical considerations:

Coprimary Objectives:

1. To demonstrate non-inferiority of the antibody response in terms of geometric mean titers (GMTs) against meningococcal serogroups A, C, W, and Y, following the administration of a 2-dose series (1+1 vaccination schedule) of MenACYW conjugate vaccine compared to a 2-dose series (1+1 vaccination schedule) of Nimenrix®, when each vaccine is administered to infants (Dose 1) at 6-7 months of age and toddlers (Dose 2) 12-13 months of age.

   Non-inferiority will be demonstrated if for each serogroup, the 2-sided 95% CI of the GMT ratio—Group 1 (MenACYW conjugate vaccine) / Group 2 (Nimenrix®)—is above 1/1.5. The 95% CIs of the ratio will be calculated using a normal approximation of log-transformed titers.

2. To demonstrate non-inferiority of the antibody response in terms of vaccine seroresponse against meningococcal serogroups A, C, W, and Y, following the administration of a 2-dose series (1+1 vaccination schedule) of MenACYW conjugate vaccine compared to a 2-dose series (1+1 vaccination schedule) of Nimenrix®, when each vaccine is administered to infants (Dose 1) at 6-7 months of age and toddlers (Dose 2) 12-13 months of age.

   Non-inferiority will be demonstrated if for each serogroup, the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is > -10%. The 95% CIs of the

difference in proportions will be computed using the Wilson Score method without continuity correction.

Secondary Objectives:

1. To compare the antibody response in terms of seroprotection as measured by hSBA against meningococcal serogroups A, C, W and Y, 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine versus Dose 1 (priming dose) of Nimenrix® in infants 6-7 months of age
2. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at Day (D)01 (baseline) before vaccination and 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants 6-7 months of age
3. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, before and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers 12-13 months of age
4. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before Dose 1 (priming dose) as infants 6 – 7 months of age and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® as toddlers at 12-13 months of age
5. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before vaccination and at 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants at 6-7 months of age
6. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, before and at 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers at 12-13 months of age
7. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before Dose 1 (priming dose) as infants 6 – 7 months of age and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® as toddlers at 12-13 months of age

*rSBA testing will be performed in a subset of participants, the first 100 participants enrolled into each study group.

No hypotheses will be tested. The analyses will be descriptive.

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

For secondary objective 1, the difference of proportions (seroprotection rates) between Group 1 and Group 2 after Dose 1 will be calculated. The 95% confidence interval (CI) of the difference of rates will be computed using the Wilson Score method without continuity correction (Newcombe method).

Safety:

The safety analyses will be descriptive.

Safety results will be described for participants in all study groups. The main parameters for the safety endpoints will be described by 95% CI using the exact binomial method (Clopper-Person method).

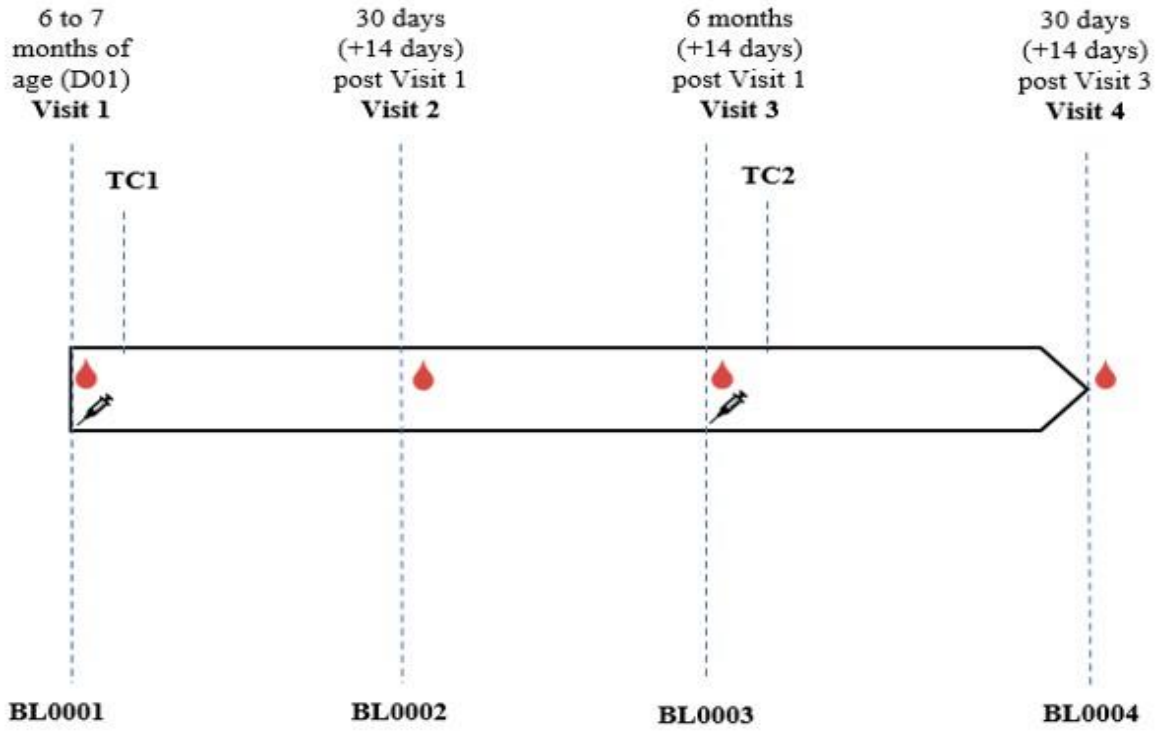
Independent Data Monitoring Committee:

No

1.2 SCHEMA

The graphical design of Study MEQ00089 is presented in Figure 1.

Figure 1: Graphical study design



BL: blood sample; D: day

TC1: safety follow-up call – 8 days post Visit 1 priming vaccination
TC2: safety follow-up call – 8 days post Visit 3 booster vaccination

: Blood Draw

: Vaccination

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1.1: Schedule of activities

Phase III Study, 4 Visits, 2 Vaccinations, 4 Blood Samples, 2 Telephone calls, ~7 to 8.5 Months' Duration Per Participant

Visit	***Collection of information in the CRF***	**Visit 1***	**TC 1††**	**Visit 2**	**Visit 3§§**	**TC 2††**	**Visit 4**
Approximate age of participants		**6 - 7 months of age**			**12 -13 months of age**		
Study timelines (days)		**D01**	**D09 Visit 1+8 days**	**D31 Visit 1+30 days**	**Visit 1+6 months**	**Visit 3+8 days**	**Visit 3+30 days**
Time windows (days)			**+2 days**	**+14 days**	**+14 days**	**+2 days**	**+14 days**
Visit procedures:							
Informed consent	X	X					
Inclusion/exclusion criteria	X	X					
Collection of demographics	X	X					
Collection of significant medical history	X	X					
Physical examination		X			X		
Pre-vaccination temperature†		X			X		
Randomization/allocation of participant number	X	X					
Review of warnings and precautions for vaccination		X			X		

Visit	***Collection of information in the CRF***	**Visit 1***	**TC 1††**	**Visit 2**	**Visit 3§§**	**TC 2††**	**Visit 4**
Approximate age of participants		**6 - 7 months of age**			**12 -13 months of age**		
Study timelines (days)		**D01**	**D09 Visit 1+8 days**	**D31 Visit 1+30 days**	**Visit 1+6 months**	**Visit 3+8 days**	**Visit 3+30 days**
Time windows (days)			**+2 days**	**+14 days**	**+14 days**	**+2 days**	**+14 days**
Review of contraindications to subsequent vaccination	X				X‡‡		
Review of temporary contraindications for blood sampling§		X		X	X		X
Blood sampling (BL) [3 mL]	X	BL0001 Pre-vac**		BL0002	BL0003 Pre-vac**		BL0004
Vaccination (vac):							
Group 1: MenACYW conjugate vaccine (IMP)	X	X			X		
Group 2: Nimenrix® (IMP)	X	X			X		
Immediate surveillance (30 min)	X	X			X		
Diary card provided		DC1		DC2	DC3		
Diary card collected				DC1	DC2		DC3
Collection of solicited injection site and systemic reactions‡	X	X	X		X	X	
Collection of unsolicited adverse events (AEs)	X	Up to 30 days after priming vaccination			Up to 30 days after booster vaccination		
Collection of adverse events of special interest	X	To be reported throughout the study					
Collection of reportable concomitant medications	X	X		X	X		X

Visit	***Collection of information in the CRF***	**Visit 1***	**TC 1††**	**Visit 2**	**Visit 3§§**	**TC 2††**	**Visit 4**
Approximate age of participants		**6 - 7 months of age**			**12 -13 months of age**		
Study timelines (days)		**D01**	**D09 Visit 1+8 days**	**D31 Visit 1+30 days**	**Visit 1+6 months**	**Visit 3+8 days**	**Visit 3+30 days**
Time windows (days)			**+2 days**	**+14 days**	**+14 days**	**+2 days**	**+14 days**
Collection of serious adverse events (SAEs)	X	To be reported throughout the study					
Collection of End of Study status***	X						X

CRF: case report form; DC: diary card; IRT: interactive response technology; IMP: investigational medicinal product; TC: telephone call

*At Visit 1, participants must be at least 6 months of age. "6 to7 months" means from the day of the 6th month after birth to the day before the 8th month after birth

†Temperature to be measured by oral, rectal, or axillary route (axillary preferred) using a standard digital thermometer and recorded in the source document

§Should a participant receive oral or injectable antibiotic therapy within 3 days prior to any blood draw, the investigator will postpone that blood draw until it has been 3 days since the participant last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw. If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

‡ Solicited injection site and systemic reactions will be recorded for 8 days from the day of each vaccination at Visit 1 and Visit 3

**Blood samples at Visit 1 and Visit 3 will be drawn before administration of the vaccine

††This call is to be made 8 to 10 days after the vaccination visit. If the contact date (+2 days) falls on a weekend or holiday, the TC may be made on the following business day. During this TC, 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. They will also find out whether the participant experienced any SAEs, including AESIs, not yet reported, and are to remind the participant's parent/legally acceptable representative to continue using the diary card (DC) up to the next visit, to bring the DC to the study center at the next visit, and to confirm the date and time of the next visit.

§§ Visit 3 is Visit 1 + 6 months meaning V1 + 180 days (+14 days). "12 to 13 months" of age at Visit 3 means from the day of the 12th month after birth to the day before the 14th month after birth

‡‡ Contraindications are included in Exclusion criteria at V01.

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

2 INTRODUCTION

MenACYW conjugate vaccine, which is licensed as MenQuadfi® (Meningococcal Polysaccharide [Serogroups A, C, Y, and W] Tetanus Toxoid (TT) Conjugate Vaccine, also identified as MenACYW-TT) is a quadrivalent meningococcal polysaccharide (PS) conjugate vaccine that contains capsular polysaccharides purified from *Neisseria meningitidis* serogroups A, C, W and Y covalently coupled to tetanus toxoid (TT) protein purified from *Clostridium tetani*. This vaccine is designed for the immunization of 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 quadrivalent meningococcal conjugate vaccine, Menactra®, where the antigens are conjugated to the diphtheria toxoid protein carrier, MenACYW conjugate vaccine is prepared using tetanus toxoid as the carrier protein. Conjugation of PS antigens to a protein carrier can induce T cell-dependent immune responses, that 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. Early Phase I/II trials including those with the final formulation have demonstrated the potential of the vaccine as an effective immunogen in all age groups from young infants to older adults (1, 2).

MenACYW conjugate vaccine is designed to cover a broader age range than that covered by Menactra® and Menomune® -A/C/Y/W-135. While Menactra® has been very successful since its licensure in 2005, it is not licensed in Europe and is not indicated in infants < 9 months of age or adults > 55 years of age. While Menactra® is currently licensed in different parts of the world, MenACYW conjugate vaccine is being developed by Sanofi Pasteur to be licensed worldwide and ultimately replace Menomune® -A/C/Y/W-135 (discontinued) and Menactra® in the global market as a quadrivalent meningococcal conjugate vaccine indicated in infants/toddlers, children, adolescents, adults, and older adults > 56 years of age.

MenACYW conjugate vaccine has gained initial licensure in many countries including in North America, Europe, Latin America, Africa, the Middle East, and Asia Pacific and is currently registered in over 75 countries (including the World Health Organization [WHO]).

The purpose of Study MEQ00089 is to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to Nimenrix® when administered as a 2-dose series (1+1 vaccination schedule) in healthy MenACYW-naïve infants aged 6 to 7 months at enrollment.

Study MEQ00089 will be conducted in several European Union countries.

2.1 STUDY RATIONALE

In the EU (centralized procedure) and in other countries outside the US, MenACYW conjugate vaccine is indicated for active immunization against IMD caused by *N. meningitidis* serogroups A, C, W, and Y with a single dose in individuals from the age of 12 months and older (precise wording may vary across countries). In the US, MenACYW conjugate vaccine is approved for

active immunization for the prevention of IMD caused by *N. meningitidis* serogroups A, C, W, and Y with a single dose in individuals 2 years of age and older.

An extension of the indication of MenACYW conjugate vaccine in the EU to include infants as young as 6 weeks of age has been planned. To this end, Study MET58 was conducted to provide clinical safety and immunogenicity data following use of the vaccine (along with routine pediatric vaccines) from 6 weeks of age with a 3-dose series (2+1 vaccination schedule), with doses administered at 2, 4 and 12 months of age in infants/toddlers, and conducted with Nimenrix® as a comparator. The primary objective of the study was to demonstrate non-inferiority of MenACYW conjugate vaccine vs Nimenrix® based on a primary endpoint of geometric mean titers (GMTs) post-booster, measured with a serum bactericidal assay using human complement (hSBA). Despite post-booster seroprotection rates (94.7%–100.0%) and seroresponse rates (90.6%–99.4%) demonstrating the clinical protection afforded by the vaccine for serogroups A, C, W, and Y, non-inferiority based on GMTs post-booster was marginally missed for serogroup A (as the lower limit of the 2-sided 95% CI of the ratio of hSBA GMTs for this serogroup was 0.565, which was below the threshold of 0.667). Of note, non-inferiority was met for serogroups C, W, and Y.

The above findings have implications for Study MEQ00089, which is the basis of this protocol amendment. Study MEQ00089 is being conducted to support a 2-dose series (1+1 vaccination schedule) in the EU for immunization of individuals from 6 months of age and is designed to evaluate the non-inferiority of the immunological response of MenACYW conjugate vaccine against the EU-approved comparator vaccine Nimenrix® after completion of the 2-dose series (1+1 vaccination schedule), with the first (priming) dose being given at 6-7 months of age to MenACWY- naïve healthy infants and the second (booster) dose given at 12-13 months of age. This study will also describe additional immunogenicity parameters and safety of MenACYW conjugate vaccine and Nimenrix® in the same population of participants. The primary objective of Study MEQ00089 is the same as that for Study MET58 (ie, to demonstrate non-inferiority of MenACYW conjugate vaccine vs Nimenrix® based on a primary endpoint of GMTs post-booster, as measured with hSBA). A comparable study (MET61) in the same age group, which was conducted in the US with Menveo® as the comparator, provides additional data to support a 1+1 immunization schedule starting at 6-7 months of age. Of note, non-inferiority in that study was based on a primary endpoint on seroresponse (instead of GMTs) post-booster, and a secondary endpoint of seroprotection post-booster.

Understanding there are no efficacy or effectiveness studies for MenQuadfi or Nimenrix® that have investigated the ability of theses vaccines to prevent actual disease, immunogenicity based on GMTs alone may not be sufficient in the evaluation of a meningococcal conjugate vaccine against a current standard of care. As stated in the European public assessment report (EPAR) at the time of MenQuadfi's initial licensure in the EU, "*Although seroprotection is considered clinically relevant for the individual subject, seroresponse is considered more relevant for the immunogenicity assessment, especially since a rather high percentage of subjects with seroprotective titres at baseline was included in the submitted studies most relevant analysis with respect to interpretation of the vaccine effect on antibody titers*" (3). Moreover, seroresponse, as currently defined in the MEQ00089 protocol, provides an opportunity to evaluate potential clinical benefit, both in terms of vaccine-induced immunity (by accounting for baseline seropositivity) and individual-level protection against invasive meningococcal disease (when one considers an hSBA threshold of ≥ 1:8) (4, 5). Accordingly, Sanofi is amending the MEQ00089

protocol to add seroresponse post-booster dose as a second primary endpoint upon which non-inferiority of MenACYW conjugate vaccine vs Nimenrix® will be assessed. In making this change, the primary objective will now become the demonstration of non-inferiority of MenACYW conjugate vaccine vs. Nimenrix® based on the primary endpoint of GMTs post-booster dose (as originally planned) along with seroresponse post-booster dose as a coprimary endpoint. Of note, the non-inferiority assessment can be conducted with the current size of the study population with a power that is >88%.

2.2 BACKGROUND

IMD occurs as a result of a systemic bacterial infection by *N. meningitidis*, a Gram-negative diplococcus found exclusively in humans. *N. meningitidis* may cause a wide range of clinical manifestations. At least 12 serogroups of *N. meningitidis* have been described based on the biochemical composition of capsular polysaccharides. Of these, serogroups A, B, C, W, X and Y cause the majority of meningococcal disease worldwide (6).

Meningococci colonize the nasopharynx of humans and are frequently harmless commensals. Carriage rates vary significantly by age, geography, and duration. Carriage rates are usually highest among adolescents ranging up to 25%, followed by young adults at between 5% and 11%. Individuals often carry the bacteria without any signs or symptoms of the disease. It is not fully understood why disease develops in some individuals but not in others. Age, season, smoking, preceding influenza A infection, mass gathering events and living in ‘closed’ or ‘semi-closed’ communities, such as university halls of residence or military barracks, have been identified as risk factors (7, 8).

Various factors are thought to contribute to the increased risk of IMD in infants. The immaturity of the immune system makes this population more susceptible to infections, and risk factors associated with IMD in general are also applicable to the increased risk in infants, including close contact with an infected individual, crowded living conditions, and exposure to smoke or viral infections (9).

Although transplacentally acquired maternal antibodies (i.e., those generated by the mother from prior colonization or exposure to bacteria with cross-reactive antigens) may provide protection in some young infants, protective levels wane within the first few months of life because these antibodies are catabolized over time (10, 11). Thus, effective strategies are needed to protect infants against IMD.

Advances have taken place in the control of meningococcal disease over the past decades through prophylactic vaccination. Based on current national vaccination recommendations in EU countries, a few countries are starting meningococcal vaccinations in infants younger than 12 months of age, such as Spain, with MenACWY vaccination recommended at 4 and 12 months of age, and Malta, with MenACWY vaccination recommended at 3 and 13 months of age. In addition, a recommendation to vaccinate infants at 6 and 12 months of age with MenACWY is expected to go into effect in France on 01 January 2025. The limited recommendations for infants are based on current epidemiology in Europe and crowded immunization schedules affecting this age group, where each new vaccine means an additional injection and appointment with a physician. There is a trend towards fewer injections and simplifying the vaccination schedule, while at the same time providing flexible schedules based on: (1) the age at which the patient will

start the course of vaccination (either from 2 months, 6 months, or 12 months of age) and (2) the other vaccines included in the immunization schedule.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks, reasonably expected 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 (SmPC).

2.3.1 Risks from Study Participation

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

Table 2.1: Identified and Potential risks of clinical significance and risk mitigation / management

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: MenACYW conjugate vaccine		
Anaphylaxis	Known important identified risk occurring at a low frequency (very rare) based on what would be common for any vaccine. One case of anaphylaxis was reported after receiving the second dose of MenACYW conjugate vaccine during the clinical development of the vaccine in 2020 in Study MET52.	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 (12-14). A review by the Institute of Medicine found inadequate evidence to	Exclusion criteria: Personal history of Guillain-Barré syndrome

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	accept or reject a causal relationship between tetanus toxoid-containing vaccines and Guillain-Barré syndrome (15). No cases with MenACYW conjugate vaccine in the completed studies.	
Bell's palsy	Important potential risk-based on post-marketing experience for other quadrivalent meningococcal conjugate 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 (16). 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.	No risk mitigation actions

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Convulsions with or without fever	Non-important identified risk observed in clinical studies and post-marketing surveillance. One case of febrile convulsions was reported as related to the vaccine after receiving the third dose of MenACYW conjugate vaccine during the clinical development of the vaccine in 2019 in Study MET42.	Exclusion criteria Close monitoring in clinical trial as an AESI
Comparator: Nimenrix®		
For all countries in the European Union: Refer to the European Medicines Agency (EMA) approved SmPC of Nimenrix® for more information regarding potential risks (17).	Identified and potential risks observed in clinical studies and/or post-marketing surveillance.	Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label.
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 (18). 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.

Appropriate medical equipment and routine emergency medications must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction. This equipment is not provided by the Sponsor.

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.

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

As with any vaccine, MenACYW conjugate vaccine and Nimenrix® 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. There is no evidence that MenACYW conjugate vaccine causes immune suppression. Therefore, the risk that a participant in this trial will contract COVID-19 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-19. However, the risk of exposure to infected people cannot be completely excluded as the participants may need to be exposed to public areas (eg, travel to/from the site and at the site).

Risk Mitigation:

- Not starting 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
Coprimary	
Immunogenicity	***Immunogenicity***
1. To demonstrate non-inferiority of the antibody response in terms of geometric mean titers (GMTs) against meningococcal serogroups A, C, W, and Y, following the administration of a 2-dose series (1+1) of MenACYW conjugate vaccine compared to a 2 - dose series (1+1) of Nimenrix®, when each vaccine is administered to infants (Dose 1) at 6-7 months of age and toddlers (Dose 2) at 12-13 months of age	1. Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assays using human complement (hSBA) at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] with MenACYW conjugate vaccine or Nimenrix®, at 12-13 months of age
2. To demonstrate non inferiority of the antibody response in terms of vaccine seroresponse against meningococcal serogroups A, C, W, and Y, following the administration of a 2-dose series (1+1) of MenACYW conjugate vaccine compared to a 2-dose series (1+1) of Nimenrix®, when each vaccine is administered to infants (Dose 1) at 6-7 months of age and toddlers (Dose 2) at 12-13 months of age	2. Vaccine seroresponse against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assays using human complement (hSBA) at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] with MenACYW conjugate vaccine or Nimenrix®, at 12-13 months of age Vaccine seroresponse is defined as follows: • For a participant with a pre-vaccination (pre-Dose 1) titer < 1:8, a post-vaccination (post-Dose 2) titer ≥ 1:16 • For a participant with a pre-vaccination (pre-Dose 1) titer ≥ 1:8, a post-vaccination (post-Dose 2) titer at least 4-fold greater than the pre-vaccination (pre-Dose 1) titer
Secondary	
Immunogenicity 1. To compare the antibody response in terms of seroprotection as measured by hSBA against meningococcal serogroups A, C, W and Y, 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate	***Immunogenicity*** 1. Antibody titers ≥ 1:8, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®

Objectives	Endpoints
vaccine versus Dose 1 (priming dose) of Nimenrix® in infants 6-7 months of age	

2. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at Day (D)01 (baseline) before vaccination and 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants 6-7 months of age	2. At Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® 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 in antibody titer from pre-vaccination to post-vaccination
	• Vaccine seroresponse, defined as follows:
	  • For a participant with a pre-vaccination (pre-Dose 1) titer < 1:8, a post-vaccination (post-Dose 1) titer ≥ 1:16
	  • For a participant with a pre-vaccination (pre-Dose 1) titer ≥ 1:8, a post-vaccination (post-Dose 1) titer at least 4-fold greater than the pre-vaccination (pre-Dose 1) titer

3. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, before and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers 12-13 months of age	3. Same endpoints as described in secondary endpoint #2 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
4. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before Dose 1 (priming dose) as infants 6 – 7 months of age and at 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® as toddlers at 12-13 months of age	4. Same endpoints (except vaccine seroresponse) as described in secondary endpoint #2 at Visit 1 before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
5. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before vaccination and 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants at 6-7 months of age	5. At Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® the following will be assessed for meningococcal serogroups A, C, W and Y as measured by rSBA:

Objectives	Endpoints

	• Antibody titers against meningococcal serogroups A, C, W, and Y
	• Antibody titers ≥ 1:8 and ≥ 1:128
	• ≥ 4-fold rise in antibody titer 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 than the pre-vaccination titer

6. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, before and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers at 12-13 months of age	6. Same endpoints as described in secondary endpoint #5 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
7. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before Dose 1 (priming dose) as infants 6 – 7 months of age and 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® as toddlers at 12-13 months of age *rSBA testing will be performed in a subset of participants, the first 100 participants enrolled into each study group.	7. Same endpoints as described in secondary endpoint #5 at Visit 1 (D0) before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
Safety 1. To describe the safety profile of MenACYW conjugate vaccine and Nimenrix® after Dose 1 (priming dose) administered to infants at 6-7 months of age and after Dose 2 (booster dose) administered at 12-13 months of age	***Safety*** 1. Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination. 2. 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 each vaccination. 3. Presence of solicited systemic reactions (pre-listed in the participant's DC and CRF) up to 7 days after each vaccination. 4. Presence of unsolicited AEs up to 30 days after each vaccination.

Objectives	Endpoints
	5. Presence of SAEs [including AESIs], throughout the trial. 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
Exploratory	
1. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before vaccination and at 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants aged 6-7 months of age according to MenB vaccination status (Men B vaccination naive or not)	1. Same endpoints as described secondary in endpoint #2 at Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not)
2. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, before and at 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers at 12-13 months of age according to MenB vaccination status (Men B vaccination naive or not)	2. Same endpoints as described in secondary endpoint #2 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not)
3. To describe the antibody response as measured by hSBA against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before Dose 1 (priming dose) as infants 6 – 7 months of age and at 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® as toddlers at 12-13 months of age according to MenB vaccination status (Men B vaccination naive or not)	3. Same endpoints as described in secondary endpoint #2 at Visit 1 before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not)
4. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, before and 30 days following the administration of Dose 1 (priming dose) of MenACYW conjugate vaccine or Nimenrix® in infants aged 6-7 months of age according to MenB vaccination status (MenB vaccination naïve or not)	4. At Visit 1 (D0) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® the following will be assessed according to MenB vaccination status (MenB vaccination naïve or not) for meningococcal serogroups A, C, W and Y as measured by rSBA:

Objectives	Endpoints

	• Antibody titers against meningococcal serogroups A, C, W, and Y
	• Antibody titers ≥ 1:8 and ≥ 1:128
	• ≥ 4-fold rise in antibody titer 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 than the pre-vaccination titer

5. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, before and 1 month following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers at 12-13 months of age according to MenB vaccination status (MenB vaccination naïve or not)	5. Same endpoints as described in exploratory endpoint #4 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not).
6. To describe the antibody response as measured by rSBA* against meningococcal serogroups A, C, W, and Y, at D01 (baseline) before vaccination and at 30 days following the administration of Dose 2 (booster dose) of MenACYW conjugate vaccine or Nimenrix® in toddlers at 12-13 months of age according to MenB vaccination status (MenB vaccination naïve or not) *rSBA testing will be performed in a subset of participants, the first 100 participants enrolled into each study group.	6. Same endpoints as described in exploratory endpoint #4 at Visit 1 before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not).

4 STUDY DESIGN

4.1 OVERALL DESIGN

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	parallel-group, 2-arm, multi-center
Phase	III
Control method	Active-controlled (control = EU licensed quadrivalent meningococcal polysaccharide conjugate vaccine, Nimenrix®)
Study population	Healthy infants and toddlers aged 6 to 7 months of age at inclusion (at Dose 1) to 12-13 months of age (at Dose 2)
Level and method of blinding	Modified double-blind
Investigational intervention assignment method	Randomization
Number of participants	Approximately 840 participants (420 per group) 6 to 7 months of age at enrollment
Intervention groups	Eligible participants will be randomized to 2 groups in a 1:1 ratio to receive 2 doses of the assigned vaccine. The first dose (priming) will be administrated at 6 to 7 months of age and the second (booster) dose at 12 to 13 months of age. Group 1: MenACYW conjugate vaccine (n=420) Group 2: Nimenrix® (n=420)
Total duration of study participation	Approximately 7 to 8.5 months (at least 7 months per participant)
Countries	Several countries in the European Union
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No. See Section 10.1.5 Committees Structure for details.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

To date, 3 quadrivalent meningococcal ACYW conjugate vaccines are approved for use in the EU based on a centralized licensing procedure: MenQuadfi®, Menveo® and Nimenrix®. Only Nimenrix® is approved for use in persons ≥ 6 weeks of age, while MenQuadfi® is approved in persons ≥ 12 months of age, and Menveo® is approved in persons ≥ 2 years of age.

There is no uniform vaccination strategy in Europe, or worldwide, and each country may have a different immunization program depending on the local epidemiology, programmatic considerations, cost-effectiveness assessments as decided by national immunization technical advisory groups. Indeed, in some countries, routine meningococcal vaccination is not recommended for any age group, while for infants and toddlers in other countries, either monovalent meningococcal C (MCC) vaccination or quadrivalent meningococcal ACWY (MCV4) vaccination is recommended exclusively. Yet in other countries, a mix of MCV4 or MCC is recommended for infants and toddlers. Finally, some countries recommend MCV4 vaccination for adolescents, alone or together with younger age groups.

Therefore, the objective is to extend the indication of MenQuadfi®, which is currently licensed from 12 months of age, to 6 weeks of age to offer a wider age indication and schedule options that can cover various vaccination strategies that exist worldwide.

The clinical development program to extend the indication of MenACYW conjugate vaccine in the EU down to 6 weeks of age includes generating clinical safety and immunogenicity data following use of the vaccine in a 3-dose series (2+1 vaccination schedule), with the first dose administered at 2 months [infants aged 6 to 12 weeks (≥ 42 to ≤ 89 days)], with Nimenrix® as the control vaccine (Study MET58).

Study MEQ00089 is designed to evaluate the non-inferiority of the immunological response of MenACYW conjugate vaccine to Nimenrix® after the completion of a 2-dose series (1+1 vaccination schedule) with the first (priming) dose given at 6-7 months of age to meningococcal ACWY- naïve healthy infants and the second (booster) dose given at 12-13 months of age, and to describe the immunogenicity and safety of MenACYW conjugate vaccine in this population with Nimenrix® as the control vaccine.

A comparable study in the same age group conducted in the US with Menveo® as the comparator (Study MET61) also provides additional data to support the 1+1 immunization schedule starting at 6-7 months of age.

4.3 JUSTIFICATION FOR DOSE

The selection of MenACYW conjugate vaccine dose used in this study (10 µg each of meningococcal capsular polysaccharides from serogroups A, C, W and Y conjugated to 55 µg of tetanus toxoid protein carrier) as well as in all Phase II and Phase III studies in the MenACYW conjugate vaccine clinical development program in infants, toddlers, children, adolescents, and adults (including older adults and the elderly) for active immunization against IMD caused by serogroups A, C, W, and Y is based on both safety and immunogenicity results from nonclinical and dose selection clinical studies (MET28, MET32 and MET39) conducted in participants

including infants and toddlers (1, 19). Results of these studies are presented in the MenACYW conjugate vaccine IB.

MET39 was an exploratory Phase II, randomized, open-label, multi-center trial that enrolled US infants and toddlers (from 6 weeks to 12 months of age) to evaluate the safety and immunogenicity profile of the investigational MenACYW conjugate vaccine when administered in 5 different schedules (2, 4, 6, and 12 months; 2, 4, 6, and 15 months; 2, 4, and 12 months; 6 and 12 months; and 12 months only) and concomitantly with licensed routine pediatric vaccines administered according to their respective approved schedules. The basis for determination of schedules to be proposed for the future Phase III studies in this age group was established from the immunogenicity analyses conducted independently for doses administered in the first year of life, doses administered in the second year of life, and cumulatively after all doses were administered. The increased immune response observed after the dose administered in second year of life following the doses administered in the first year of life also highlights the importance of completing the infant immunization series and the role of the booster dose in maintaining the high levels of antibodies observed after primary vaccination.

The same formulation is also undergoing numerous additional infant and toddler clinical trials exploring the safety and immunogenicity of different vaccination sequences.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if the participant has completed the last visit planned in the SoA (Table 1.1).

The end of the study is defined as the date that the last test results have been released for samples collected at Visit 4, related to coprimary and secondary endpoints. The end of the study must be achieved no later than 9 months after the last visit of the last participant in the study.

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

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I01: Aged 6 to 7 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

Informed Consent

I03: 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

I04: Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

I05: 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:

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)

[a] "6 to7 months" means from the day of the 6th month after birth to the day before the 8th month after birth

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(s) used in the study or to a product containing any of the same substances[a]

E07: Laboratory-confirmed thrombocytopenia, or 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[b]

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

Prior/concomitant therapy

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

E12: Previous vaccination against meningococcal A, C, W, or Y disease with either the trial vaccine or another vaccine (i.e., mono- or quadrivalent meningococcal conjugate vaccines) containing serogroups A, C, Y, or W).

E13: Receipt of immune globulins, 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

---

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

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

Prior/concurrent clinical study experience

E15: Participation at the time of study enrollment (or in the 4 weeks preceding the first 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 participants parent(s) / legally acceptable representative(s)'s consent to inform this physician 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 has consented to participate in the clinical study is not subsequently assigned to study intervention. Screening information is recorded in the source documents.

In certain circumstances, 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).

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/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 10.5: Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for enrollment/randomization/administration of the study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, investigational and non-investigational/auxiliary medicinal products, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

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 6.9). 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)	**Nimenrix®:** Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited, Ramsgate Rd, Sandwich, Kent, CT13 9NJ, United Kingdom)
Intervention Description	ATC Code: J07AH08	ATC Code: J07AH08
Marketing authorization status	Approved (EU Centralized Procedure). Pharmaceutical form, qualitative and quantitative composition in accordance with the terms of the current Marketing Authorization. Age population and posology in the clinical study differ from the terms of the current Marketing Authorization.	Approved and used in accordance with the terms of the marketing authorizations
Use	Experimental	Active comparator
IMP or NIMP/AxMP	IMP	IMP
Type	Vaccine	Vaccine
Dosage Form	Solution for injection (in a single-dose vial)	Solution for injection (powder or cake in a single-dose glass vial and a clear and colorless solvent in a pre-filled syringe for reconstitution).

Intervention Name	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)	**Nimenrix®:** Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited, Ramsgate Rd, Sandwich, Kent, CT13 9NJ, United Kingdom)
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 W*: 10 µg • Serogroup Y*: 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*	After reconstitution, each 0.5 mL dose of Nimenrix® contains: *Neisseria meningitidis* polysaccharides: • Serogroup A*: 5 µg • Serogroup C*: 5 µg • Serogroup W-135*: 5 µg • Serogroup Y*: 5 µg *conjugated to tetanus toxoid protein carrier 44 µg
Excipients/Diluent	Sodium acetate buffered saline solution	Sodium chloride and water solution for reconstitution
Dosage Level(s)	0.5 mL per dose	0.5 mL per dose
Number of Doses / Dosing Interval	2 doses: Dose 1 (priming dose) at 6-7 months of age and Dose 2 (booster dose) at 12-13 months of age	2 doses: a priming dose (Dose 1) at 6-7 months of age and a booster dose (Dose 2) at 12-13 months of age
Route of Administration	IM injection	IM injection
Site of Administration	Anterolateral area of the thigh or deltoid muscle	Anterolateral area of the thigh or deltoid muscle
Injection Site Side	Right or left	Right or left
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each study intervention MenACYW conjugate vaccine will be provided in an individual box. Each study intervention (vial) will bear one fixed commercial label and each box will bear one fixed label containing the dose number. All will be labeled as required per country requirement. Each study intervention Nimenrix® will be provided in an individual box. Each study intervention (vial containing powder and pre-filled syringe) will bear one fixed commercial label and each box will bear one fixed label containing the dose number. All will be labeled as required per country requirement.	

Intervention Name	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)	**Nimenrix®:** Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited, Ramsgate Rd, Sandwich, Kent, CT13 9NJ, United Kingdom)
Current/Former Name(s) or Alias(es)	MenQuadfi®	Nimenrix®
Batch Number	TBD	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

Table 6.2 summarized the study interventions per arm.

Table 6.2: Study Arm(s)

Arm title	Group 1	Group 2
Arm type	Experimental	Active comparator
Associated study interventions	MenACYW Conjugate Vaccine	Nimenrix®
Arm description	Participants will receive **MenACYW Conjugate Vaccine:** 2-dose schedule (1+1); Dose 1 (priming dose) at 6-7 months of age and Dose 2 (booster dose) at 12-13 months of age	Participants will receive **Nimenrix®:** 2-dose schedule (1+1); Dose 1 (priming dose) at 6-7 months of age and Dose 2 (booster dose) at 12-13 months of age

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

MenACYW conjugate vaccine is supplied in single-dose (0.5 mL) vials. Nimenrix® is supplied as a white powder or cake in a single-dose vial and a clear colorless solvent in a pre-filled syringe for reconstitution and injection. Detailed instructions will be provided to the site personnel.

Both vaccines will be administered intramuscularly in the deltoid muscle of the upper arm or the anterolateral area of the thigh 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 conditions (eg, temperature) 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, prepare, or administer study intervention.
3) 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.
4) The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5) Further guidance and information for the final disposition of unused study interventions will be provided to the study personnel.

6.3 ASSIGNMENT TO STUDY INTERVENTION

Participants will be randomized.

On the day of enrollment, participants who meet all the inclusion criteria but none of the exclusion criteria and whose parent/ legally acceptable representative signs the informed consent form (ICF) will be randomly assigned to Groups 1 and 2 in a 1:1 allocation ratio, such that Groups 1, and 2 will have approximately 420 participants each. Randomization will be stratified by country.

Site staff will connect to the interactive response technology (IRT), enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the group assignment and have the site staff confirm it. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Participant numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). For example, Participant 840000100005 is the fifth participant enrolled in Center Number 1 in the US (840 being the US country code). Participant numbers should not be reassigned for any reason.

Each participant will be vaccinated with the study intervention(s) corresponding to the group mentioned on the randomization list. If the dose initially taken for the vaccination is broken or cannot be used, the investigator will take another dose of the same study intervention.

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT.

6.4 BLINDING

The study will be performed in a modified double-blind fashion:

- Investigators and study staff who conduct the safety assessment and the participants parent/ legally acceptable representative will not know which study intervention is administered
- The IRT vendor will be responsible for providing the treatment group identification for the enrolled participants
- Only the study staff who prepare and administer the study intervention and are not involved with the safety evaluation will know which study intervention is administered
- Until the data base is locked the laboratory personnel performing the serology testing will also be blinded to the group assignments and will follow a written procedure detailing how the blind will be maintained

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

The blind can be broken by the investigator or a designee through the IRT system. Once the emergency has been addressed by the site, the investigator or a designee must notify the Sponsor's RMO if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking case report form (CRF) is to be completed.

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

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

- by the Patient Safety and Pharmacovigilance(PSPV) Department through an internal system for reporting to Health Authorities in the case of an unexpected SAE considered causally related, as described in International Council for Harmonisation (ICH) E2A[a]. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant's study intervention or group assignment) will not be communicated to either the investigator or the immediate team working on the study, except for the GPV representative.

[a] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

6.5 STUDY INTERVENTION COMPLIANCE

The following measures will ensure that the study intervention is administered as planned (see Section 10.5), 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 Section 10.5: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

6.6 DOSE MODIFICATION

Not applicable.

6.7 CONTINUED ACCESS TO STUDY INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.8 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) Evaluate the participant to determine, in consultation with the RMO, whether study intervention should be interrupted.
3) Closely monitor the participant for any AE/SAE.
4) Document the quantity of the excess of the overdose in the source documents.

See also Section 8.4.7 for the reporting.

6.9 PRIOR AND CONCOMITANT THERAPY

Prior and concomitant therapy collected includes medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an AE) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain

bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

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

The following reportable medications are defined:

- 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).
  Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.
- Medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Sponsor's laboratory or other testing laboratories, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors).
- Medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

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

Prophylactic use of antipyretic in pediatric population to reduce the incidence and severity of fever specifically in conjunction with routine vaccination will be allowed and will be collected in a specific CRF Form.

Reason for treatment, route, dose, frequency, 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 or blood puncture sites).

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 WHO Drug dictionary.

Protocol-prohibited therapy will lead to exclusion from the per-protocol analysis set. The following medications will be prohibited:

- Immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, received within 6 months before a study vaccination; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) within the 3 months before a study vaccination or study visit with collection of blood for immunogenicity assessments.

- Any vaccine (including COVID-19 and MenB vaccines) received in the 4 weeks preceding the first and second study intervention administration or in the 4 weeks following any study intervention administration except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after the study interventions.
- Any vaccination against meningococcal disease with either the trial vaccines or another vaccine (ie, mono- or quadrivalent conjugate meningococcal vaccine) containing serogroups A, C, Y, or W outside of the study protocol.
- Oral or injectable antibiotic therapy received within 72 hours prior to an immunogenicity blood draw.
- Immune globulins, blood, or blood-derived products received within 3 months before a study vaccination or study visit with collection of blood for immunogenicity assessments.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 10.1.9.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Temporary Contraindications

Should a participant experience one of the conditions listed below, the investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the SoA (Table 1.1).

If the postponement occurs out of the timeframe for vaccination, the participant can continue to receive study intervention but will be excluded from the per-protocol analysis set (see Section 9.2).

TCI01: 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.

TCI02: Receipt of any vaccine (including COVID-19 and MenB vaccines) in the 4 weeks preceding the first and second study intervention administration or in the 4 weeks following any study intervention administration except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study intervention. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

TCI03: Systolic blood pressure, diastolic blood pressure or pulse rate outside the normal ranges as part of the physical examination at the time of vaccination.

Temporary intervention discontinuation may be considered by the investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 10.5: Contingency Measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the investigator in the source documents.

In addition, for a regional or national emergency declared by a governmental agency, how long the temporary discontinuation will be allowed should be specified, its impact on the study conduct should be considered.

7.1.2 Definitive Contraindications

Participants will permanently discontinue (definitive discontinuation) study intervention for the reasons listed below. These participants must not receive any additional dose of study intervention but should continue to be followed for safety.

Should a participant experience at least one of the conditions listed below, the investigator will discontinue further vaccination:

DCI01: Severe allergic reaction (e.g., anaphylaxis) after a previous dose of vaccine, any component of the vaccine, or any other tetanus toxoid or meningococcal-containing vaccine.

DCI02: For infants / toddlers: Febrile seizures at least possibly related to the investigational product, as assessed by the Investigator or the Sponsor

DCI03: SAE assessed as related to the study vaccine following the previous dose of vaccine, based on investigator's judgment

DCI04: Injection site necrosis, ulceration, or abscess

DCI05: Thrombocytopenia or bleeding disorder, which may be a contraindication for IM vaccination, based on the investigator's judgment

In the event of a local or national immunization program with a pandemic influenza vaccine, SARS-CoV-2 or a COVID-19 pandemic vaccine, participants who receive the vaccine mentioned above at any time during the study will not be withdrawn from the study.

7.1.3 Other Reasons

A participant may discontinue from study intervention at any time at the participant's parent(s)/legally acceptable representative(s) request, for any reason (or without providing any reason).

A participant may discontinue from study intervention at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Participants should continue to be followed for safety.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's parent(s)/legally acceptable representative(s) request, for any reason (or without providing any reason).
- A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- 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 the participant's parent(s)/legally acceptable representative(s) and complete all scheduled safety follow-ups, except if the participant's /parent(s)/legally acceptable representative(s) specified that they do not want to be contacted again and it is documented in the source document.

- If the participant's parent(s)/legally acceptable representative(s) withdraw consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant's parent(s)/legally acceptable representative(s) withdraw from the study, the participant's parent(s)/legally acceptable representative(s) may request destruction of any samples taken and not tested (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 the participant repeatedly fails to return for scheduled visits and the participant's parent(s)/legally acceptable representative(s) 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 the participant's parent(s)/legally acceptable representative(s) cannot be contacted as planned in the SoA (Table 1.1):

- The site must attempt to contact the participant's parent(s)/legally acceptable representative(s) and reschedule the missed visit as soon as possible, counsel the participant's parent(s)/legally acceptable representative(s) on the importance of maintaining the assigned visit schedule and ascertain whether the participant's parent(s)/legally acceptable representative(s) wish to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant's parent(s)/legally acceptable representative(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's parent(s)/legally acceptable representative(s) last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant's parent(s)/legally acceptable representative(s) 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 (Table 1.1). Protocol waivers or exemptions are not allowed.
- 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.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- 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.

8.1 ADMINISTRATIVE AND GENERAL PROCEDURES

8.1.1 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).

8.1.2 Sample Collection

Blood samples will be collected as described in the SoA table for immunogenicity assessments (Section 1.3). Pain relieving remedies such as topical analgesics (gel or patches applied at the blood puncture site) or oral sugar solutions may be offered to the participants at the discretion of the investigator and according to local practices. The use of topical analgesics at blood puncture sites will be recorded in the CRF.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 12 mL, with 3 mL of blood collected from each participant at Visit 1 (BL0001), Visit 2 (BL0002), Visit 3 (BL0003), and Visit 4 (BL0004).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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.

8.2 EFFICACY AND IMMUNOGENICITY ASSESSMENTS

Planned timepoints for all immunogenicity assessments are provided in the SoA (Table 1.1).

8.2.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.2.2 Immunogenicity Assessments

Assays will be performed by the Sponsor's laboratory or an external testing laboratory under the Sponsor's laboratory responsibility.

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. Only a subset of samples in each group will be tested by rSBA (first 100 participants randomized in each group).

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 (CO2). 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 a Sanofi laboratory or at qualified contract laboratories under Sanofi laboratory responsibility.

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). The LLOQ of the rSBA assay is a titer of 1:4.

The rSBA testing will be performed at United Kingdom Health Security Agency, Manchester, (Pr Ray Borrow), United Kingdom.

Only a subset of samples in each group will be tested by rSBA (first 100 participants randomized into each of the study groups to have 4 blood draws). In the event of insufficient serum sample volume, the conduct of the hSBA assay is of higher priority than the rSBA assay.

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4.

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

8.3.1 Physical Examinations

At each visit, the investigator or a designee will perform a clinical or medically-driven physical examination. Information will be recorded in the source document.

8.3.2 Vital Signs

Axillary pre-vaccination body temperature will be systematically collected by the investigator on the source document, including the route of measurement. Tympanic, skin, and temporal artery thermometers must not be used.

8.4 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 participant's 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). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative).

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.

8.4.1 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 each 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 each vaccination (ie, From Visit 1 to Visit 1+8 days (D01 to D08) and from Visit 3 to Visit 3+8 days).

Solicited systemic reactions will be collected from the day of vaccination until 7 days after each vaccination (ie, From Visit 1 to Visit 1+8 days (D01 to D08) and from Visit 3 to Visit 3+8 days).

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 IMP vaccination until 30 days after each IMP vaccination.

The intensity grading scale for unsolicited non-serious adverse events is presented in Appendix 10.2.5.2.

Adverse Events of Special Interest (AESIs)

AESIs will be collected throughout the study period from Visit 1 vaccination to Visit 4 (+14 days).

See Section 8.4.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from inclusion (Visit 1) until Visit 4 (+14 days), ie, 30 days (+14 days) after the last 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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.4.2 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 body 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.

8.4.3 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 refuse 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 8.4.6)], 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 and related AESIs 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.

8.4.4 Regulatory Reporting Requirements for SAEs and Other Safety Reporting

- 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/or other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with international/regional and country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), 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.

For the European Union, safety reporting to the agency is described in Section 10.4.1.1.

8.4.5 Pregnancy

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

8.4.6 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) (20)
- Kawasaki disease (21-23)
- Guillain-Barré syndrome (24)
- Idiopathic thrombocytopenic purpura (ITP) (25)

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.

8.4.7 Medication Errors, Misuses or Abuses of Medicinal Product

Definitions of medication error, misuse or abuse can be found in Appendix 10.3.

Since the study intervention*s* are administered by a health care professional, misuse and abuse are not applicable in this study. Medication errors will be recorded in the GPV database.

8.5 PHARMACOKINETICS

Pharmacokinetics parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamics parameters are not evaluated in this study.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

No other biomarkers than those described in the immunogenicity assessments section (Section 8.2.2) are evaluated in this study.

8.9 IMMUNOGENICITY ASSESSMENTS

See Section 8.2.2.

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

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

8.11 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. Relating data will be stored for up to 25 years.

The other biological samples collected to qualify the participants for inclusion in the study or to monitor their 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.

8.12 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 participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of samples will not be included in the local 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 the ICF. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Study participant data for future research will be stored for up to 25 years after the end of the study.

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 the human biological samples (leftover) in 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 participants request destruction of their 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

Statistical analyses of endpoints may be performed in 1 step (including all endpoints, reported in 1 CSR) or 2 steps as follows, if a significant delay (more than 9 months after the last visit of the last participant) in the availability of rSBA data are encountered:

- A first statistical analysis / CSR will be generated including hSBA immunogenicity data and all safety data from all participants
- A second statistical analysis will be performed for rSBA endpoints and discussed in an addendum to the first CSR)

The statistical analysis plan (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 the most important endpoints including coprimary and key secondary endpoints.

9.1 STATISTICAL HYPOTHESES

The coprimary objectives will be met if the following coprimary hypotheses are rejected.

Coprimary Objectives

- **Primary Hypothesis 1 (MenACYW antibody titers [geometric mean titers (GMTs)] after Dose 2)**

Non-inferiority of MenACYW conjugate vaccine (Group 1) compared to Nimenrix® (Group 2) in terms of hSBA antibody titers after a 2-dose series to toddlers at 12 months of age will be tested.

For each of the 4 serogroups (A, C, W, and Y), GMTs 30 days after a 2-dose series vaccination will be used to compare Group 1 and Group 2 with the following individual hypotheses:

H0 (Null hypothesis):

- $GMT_{MenACYW} / GMT_{Nimenrix} \leq 1/1.5$ (or $GMT_{Nimenrix} / GMT_{MenACYW} \geq 1.5$)

H1 (Alternative hypothesis):

- $GMT_{MenACYW} / GMT_{Nimenrix} > 1/1.5$ (or $GMT_{Nimenrix} / GMT_{MenACYW} < 1.5$)

Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. For each serogroup, the 2-sided 95% CI of the GMT ratio Group 1 (MenACYW) / Group 2 (Nimenrix®) should lie above 1/1.5.

- **Primary Hypothesis 2 (MenACYW vaccine seroresponse after Dose 2)**

Non-inferiority of MenACYW conjugate vaccine (Group 1) compared to Nimenrix® (Group 2) in terms of hSBA vaccine seroresponse after a 2-dose series to toddlers at 12 months of age will be tested.

For each of the 4 serogroups (A, C, W, and Y), vaccine seroresponse 30 days after a 2-dose series vaccination will be used to compare Group 1 and Group 2 with the following individual hypotheses:

H0 (Null hypothesis):

- $p(_{MenACYW}) - p(_{Nimenrix}) \leq -10\%$

H1 (Alternative hypothesis):

- $p(_{MenACYW}) - p(_{Nimenrix}) > -10\%$

  where $p(_{MenACYW})$ and $p(_{Nimenrix})$ are the % of participants who achieve an hSBA vaccine seroresponse in the MenACYW conjugate vaccine group and the Nimenrix® group, respectively.

Each of the serogroups A, C, Y, and W will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected.

Vaccine seroresponse is defined as follows:

- For a participant with a pre-vaccination (pre-Dose 1) titer < 1:8, a post-vaccination (post-Dose 2) titer ≥ 1:16
- For a participant with a pre-vaccination (pre-Dose 1) titer ≥ 1:8, a post-vaccination (post-Dose 2) titer at least 4-fold greater than the pre-vaccination titer

Secondary and exploratory objectives

No hypotheses will be tested. The analyses will be descriptive.

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

Reverse cumulative distribution curve (RCDC) figures may be also provided.

For secondary objective 1, the difference of proportions (seroprotection rates) between Group 1 and Group 2 after Dose 1 will be calculated. The 95% CI of the difference of the rates will be computed using the Wilson Score method without continuity correction.

9.1.1 Multiplicity Adjustment

Not applicable.

9.2 ANALYSIS SETS

In this study, antibody titers will be measured with 2 different methods: hSBA or rSBA.

Coprimary, secondary and exploratory endpoints will be analyzed according to the type of measurement and also according to the doses and timepoints of administration: Dose 1 (priming dose) / Dose 2 (booster dose). Several analysis sets will be used for the analyses as follows:

	To assess Dose 1 (BL0002)		**To assess Dose 2 (BL0004)**		**To assess the 2-dose schedule (BL0004)**	
Measurement	**hSBA**	**rSBA**	**hSBA**	**rSBA**	**hSBA**	**rSBA**
Analysis set to use	hSBA PPAS1	rSBA PPAS1	hSBA PPAS2	rSBA PPAS2	hSBA PPAS2	rSBA PPAS2
	hSBA FAS1	rSBA FAS1	hSBA FAS2	rSBA FAS2	hSBA FAS2	rSBA FAS2

Note: rSBA testing will be performed in a subset of the first 100 participants enrolled into each study group.

The safety analyses will be performed on the overall SafAS, SafAS1 and SafAS2. Participants will be analyzed according to the vaccine they actually received.

9.2.1 Full Analysis Set (FAS)

There will be 4 FASs, 2 FASs for the priming vaccination (hSBA FAS1 and rSBA FAS1) and 2 FASs for the booster vaccination (hSBA FAS2 and rSBA FAS2).

FAS based on hSBA measurements:

- hSBA FAS1 (for Dose 1 [priming dose]) is defined as the subset of randomized participants who received a dose of the study vaccine at V1 and had a valid post-vaccination hSBA result at V2.
- hSBA FAS2 (for Dose 2 [booster dose]) is defined as the subset of randomized participants who received a dose of the study product at V3 and had a valid post-booster vaccination hSBA result at V4.

FAS based on rSBA measurements:

- rSBA FAS1 (for Dose 1 [priming dose]) is defined as the subset of randomized participants who received a dose of the study vaccine at V1 and had a valid post-vaccination rSBA result at V2.
- rSBA FAS2 (for Dose 2 [booster dose]) is defined as the subset of randomized participants who received a dose of the study vaccine at V3 and had a valid post-booster vaccination rSBA result at V4.

9.2.2 Per-Protocol Analysis Set (PPAS)

The PPAS is a subset of the FAS. There will be 4 PPASs: 2 PPAS for the priming vaccination (hSBA PPAS1 and rSBA PPAS1) and 2 PPAS for the booster vaccination (hSBA PPAS2 and rSBA PPAS2). PPAS based on hSBA measurements:

- hSBA PPAS1 (for Dose 1 [priming dose] ; BL0002)
- hSBA PPAS2 (for Dose 2 [booster dose] ; BL0004)

PPAS based on rSBA measurements:

- rSBA PPAS1 (for Dose 1 [priming dose] ; BL0002)
- rSBA PPAS2 (for Dose 2 [booster dose] ; BL0004)

The definitions of all PPASs are detailed in Section 9.2.2.1 to Section 9.2.2.4.

9.2.2.1 hSBA PPAS for Dose 1 (priming dose)

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the hSBA PPAS1 for the priming dose:

- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Participant did not receive Dose 1 (priming dose)

- Participant received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Participant did not receive vaccine in the proper time window
- Participant did not provide serology samples in the proper time window post-Dose 1 vaccination
- Post-Dose 1 vaccination serology samples were not drawn
- Participant received a protocol-prohibited therapy / medication / vaccine
- Serology samples did not produce a valid hSBA result (ie, results for all antigens are missing)
- Participant had other protocol violations that may have affected the participant's immune response, as determined by the clinical team before locking the database

9.2.2.2 hSBA PPAS2 for Dose 2 (booster dose)

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the hSBA PPAS2 for the booster dose:

- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Participant did not receive Dose 2 (booster dose)
- Participant received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Participant did not receive vaccine in the proper time window
- Participant did not provide serology samples in the proper time window post-Dose 2 vaccination
- Post-Dose 2 vaccination serology samples were not drawn
- Participant received a protocol-prohibited therapy / medication / vaccine
- Serology samples did not produce a valid hSBA result (ie, results for all antigens are missing)
- Participant had other protocol violations that may have affected the participant's immune response, as determined by the clinical team before locking the database

9.2.2.3 rSBA PPAS1 for Dose 1 (priming dose)

The definition of the rSBA PPAS1 is the same as for the hSBA PPAS1 except for the following criterion:

- Serology samples did not produce a valid rSBA result (ie, results for all antigens are missing)

9.2.2.4 rSBA PPAS2 for Dose 2 (booster dose)

The definition of the rSBA PPAS2 is the same as for the hSBA PPAS2 except for the following criterion:

- Serology samples did not produce a valid rSBA result (ie, results for all antigens are missing)

In the event of a local or national immunization program with a pandemic influenza vaccine, participants who receive 1 or more doses of a pandemic influenza vaccine at any time during the study will not be withdrawn from the study.

9.2.2.5 Safety Analysis Set

The safety analysis set (SafAS) is defined as those participants who have received at least one dose of the study vaccine(s) and have any safety data available. All participants will have safety analyzed after each dose according to the vaccine they received, and after any dose according to the vaccine received at the first dose. Safety data recorded for a vaccine received outside of the protocol design will be excluded from the analysis (and listed separately).

9.2.2.5.1 Overall Safety Analysis Set for Any Dose

The overall SafAS is defined as those participants who have received at least one dose of the study vaccines and have any safety data available. All participants will have their safety analyzed after any dose according to the vaccine received at the first dose.

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

9.2.2.5.2 Safety Analysis Set for Vaccination at 6 Months of Age

The SafAS1 for vaccination at 6-7 months of age is defined as those participants who have received the study vaccine at Visit 1 and have any safety data available. All participants will have their safety analyzed after the Visit 1 dose according to the vaccines they actually received at visit 1.

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

9.2.2.5.3 Safety Analysis Set for Vaccination at 12 Months of Age

The SafAS2 for vaccination at 12-13 months of age is defined as those participants who have received the study vaccine at Visit 3 and have any safety data available. All participants will have their safety analyzed after the Visit 3 dose according to the vaccines they actually received at Visit 3.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis.

9.3 STATISTICAL ANALYSES

9.3.1 General Considerations

All immunogenicity analyses will be performed on the PPAS and on the FAS. All safety analyses will be performed on the SafAS. Unless otherwise specified, analyses will be performed by intervention group and overall for baseline and demographic characteristics.

9.3.2 Coprimary Endpoint Analysis

The coprimary endpoints for the evaluation of immunogenicity are:

1. Antibody titers (geometric mean titers [GMTs]) against meningococcal serogroups A, C, W, and Y measured by hSBA after the administration of a 2-dose series (1+1 vaccination schedule) with MenACYW conjugate vaccine or Nimenrix®.

   Assuming that Log10 transformation of the data follows a normal distribution, the Log10 (data) will be used for the statistical analysis and antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMT.

   The statistical methodology will be based on the use of the 2-sided 95% confidence interval (CI) of the ratio of post-vaccination GMTs between Group 1 and Group 2. The CI will be calculated using a normal approximation of log-transformed titers.

   Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. For each serogroup, the 2-sided 95% CI of the GMT ratio Group 1 (MenACYW) / Group 2 (Nimenrix®) should lie above 1/1.5.

2. Vaccine seroresponse against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assays using human complement (hSBA) at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] with MenACYW conjugate vaccine or Nimenrix®, at 12-13 months of age.

   If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected.

   For the non-inferiority hypotheses using seroresponse rates, the CI of the difference in proportions is computed using the Wilson Score method without continuity correction.

There are no primary safety endpoints.

9.3.3 Secondary Endpoints Analysis

No hypotheses will be tested. The analyses will be descriptive.

Secondary immunogenicity endpoints will include the following:

1. Antibody titers ≥ 1:8, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
2. At Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® 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 in antibody titer 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 than the pre-vaccination titer
3. Same endpoints as described in secondary endpoint #2 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
4. Same endpoints as described in secondary endpoint #2 at Visit 1 before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
5. At Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® 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 in antibody titer 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 than the pre-vaccination titer

6. Same endpoints as described in secondary endpoint #5 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®
7. Same endpoints as described in secondary endpoint #5 at Visit 1 (D0) before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix®

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

For secondary objective 1, the difference of titers between Group 1 and Group 2 in terms of seroprotection after Dose 1 will be calculated. The 95% CI of the difference of rates will be computed using the Wilson Score method without continuity correction (Newcombe method).

9.3.4 Exploratory Endpoints Analysis

1. Same endpoints as described secondary in endpoint #2 at Visit 1 (D01) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not)
2. Same endpoints as described in secondary endpoint #2 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not)
3. Same endpoints as described in secondary endpoint #2 at Visit 1 before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not)
4. At Visit 1 (D0) before Dose 1 (priming dose) and at Visit 2, 30 days after Dose 1 (priming dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® the following will be assessed according to MenB vaccination status (MenB vaccination naïve or not) 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 in antibody titer 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 than the pre-vaccination titer

5. Same endpoints as described in exploratory endpoint #4 at Visit 3 before Dose 2 (booster dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not).
6. Same endpoints as described in exploratory endpoint #4 at Visit 1 before Dose 1 (priming dose) and at Visit 4, 30 days after Dose 2 (booster dose) [+14 days] of MenACYW conjugate vaccine or Nimenrix® by MenB vaccination status (MenB vaccination naive or not).

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

9.3.5 Safety Analysis

Secondary safety endpoints will include at least the following:

1. Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination.
2. 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.
3. Presence of solicited systemic reactions (pre-listed in the participant's DC and CRF) up to 7 days after vaccination.
4. Presence of unsolicited AEs up to 30 days after vaccination.
5. Presence of SAEs [including AESIs], throughout the trial.

Safety results will be described for participants in all study groups. The main parameters for the safety endpoints will be described by 95% CI using the exact binomial method (Clopper-Person method).

9.3.6 Other Analysis

Not applicable.

9.4 INTERIM ANALYSES

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

This study will not include an early safety data review.

9.5 SAMPLE SIZE DETERMINATION

A total of approximately 840 (420 per group) participants are planned to be enrolled with the aim to obtain a total of 672 (336 per group) evaluable participants.

For Coprimary Objective 1:

With 420 enrolled participants in Group 1 and in Group 2, the study will have > 90% power to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, and Y hSBA antibody titers (ratio of GMTs in the 2 groups) after a 2-dose series to toddlers at 12 months of age, assuming a:

- 20% dropout rate from the PPAS (336 participants evaluable by group),
- 1-sided alpha level of 2.5%,
- a non-inferiority margin of 1.5 (GMT ratio),
- Standard deviation (SD) of log10-transformed titers of 0.6 for serogroups A, C and W, and 0.5 for serogroup Y

For Coprimary Objective 2:

With 420 evaluable participants in Group 1 and in Group 2, the study will have 98.37% power by using the Farrington and Manning's method to declare the non-inferiority of Group 1 vs Group 2 based on A, C, W, and Y hSBA vaccine seroresponse in the 2 groups, after a 2-dose series to toddlers at 12 months of age, assuming a:

- 20% dropout rate from the PPAS (336 participants evaluable by group),
- 1-sided alpha level of 2.5%,
- a non-inferiority margin of 10% (percentage difference)

Power of the study for the coprimary objectives:

The study will have 88.53% overall power to declare the non-inferiority based on the coprimary objectives.

Coprimary Objective#	Antigen	MenACYW conjugate vaccine Estimated Standard Deviation*/Response†	Non-inferiority margin	Power (%)
Coprimary Objective 1	A	0.6	1.5	96.7
	C	0.6	1.5	96.7
	W	0.6	1.5	96.7
	Y	0.5	1.5	99.5
	Overall			≥ 90%
Coprimary Objective 2	A	89.4%	10%	98.37
	C	99.3%	10%	100
	W	98.6%	10%	100
	Y	99.3%	10%	100
	Overall			98.37%
Overall, for Coprimary Objectives				88.53%

Since the hypothesis needs to be met for all serogroups, no alpha adjustment for multiple comparisons is necessary in these calculations.
* Standards deviations are based on the MET39 study results.
† Vaccine responses are based on results from Study MET61.
A non-inferiority margin of 10% has been widely used in previous studies evaluating the same antigens.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Note: The term "participant" is used throughout this protocol and in the DC. 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 the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws
  - Any other laws and regulations as applicable, eg:
    - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use
    - 21 CFR
- The protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants
- If appropriate (based on local regulation) the following list of investigator responsibilities can be modified to reflect situations where the responsibility is shared with the Sponsor. An example is provided where centralized IRBs require written summaries on the status of the study from both the Investigator and the Sponsor
- The investigator will be responsible for the following, as applicable:
  - 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, if applicable

- 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 their 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 ICH guidelines, the IRB/IEC, and if applicable, 21 CFR, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

As applicable, according to requirements of the Regulation No 536/2014 of the European Parliament and the Council of the European Union, 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.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EAA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect

to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

The Sponsor shall ensure that all parties involved in the conduct of the clinical study promptly report any events that might meet the definition of a serious breach.

Therefore, investigators shall, within 48 hours after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal investigator must have a process in place to ensure that the site staff or service providers engaged by the principal investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The ICF will be provided to the study participant in paper version.
- The investigator or the investigator's representative will explain the nature of the study, including the potential risks and benefits, to the participants' parents / legally acceptable representatives and answer all questions regarding the study, including what happens to the participants when their participation ends (post-trial access strategy for the study).
- Potential participants' parents / legally acceptable representatives must be informed that their child's participation is voluntary. Participants' parents / legally acceptable representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements including those of the GDPR and of the French law, where applicable, and the IRB/IEC or study center.
- If applicable, state that the presence of 1 or more witnesses is required for all participants.
- Based on the local regulations, the presence of 1 or more witnesses may be required.
- 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 participation in the study, this will

be communicated to them 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 participants' parents / legally acceptable representatives.

The core ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones). Future research is to be defined in the core ICF Part 2. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in the core 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; and consent for performance of genetic analyses on biological samples. The investigator or authorized designee will explain to each participant why data and samples are important for future research. Participants 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

MEQ00089 is a study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine with Nimenrix® when administered in a 2-dose series (1+1 schedule) in healthy infants and toddlers at 6 and 12 months of age (see Section 2.1 Study Rationale)

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.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.5: 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. 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 will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participants' parents/legally acceptable representatives identifiable will not be transferred to the Sponsor.
- 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 as described in the informed consent.
- 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.
- The contract between Sponsor, investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of participants concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- 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 personal 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 25 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 request the 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 - 46 Avenue de la Grande Armée - 75017 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 (Safety Management Team [SMT]) which includes safety signal detection at any time during the study. SMT will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The Sponsor's internal SMT led by the PV representative and the RMO, will be responsible for the blinded 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.

This study will not include an early safety data review; ie, no early safety reviews of preliminary safety data occurring at pre-determined milestones defined in the protocol, with pause in enrollment is planned for this trial as MenACYW conjugate vaccine has been previously administered to infants, toddlers, and adults, with an acceptable safety profile and no unexpected safety concerns have been identified in the clinical trials completed to date. About 10,585 participants from 6 weeks to 23 months of age have been exposed to MenACYW conjugate vaccine and have received at least one injection in completed or ongoing clinical trials evaluating multiple dose schedules of the product (4 doses or 3 doses when the first dose is administered approximately 2 months of age, and 2 doses when the first dose is administered approximately 6 months of age), and single-dose when the vaccine is administered in toddlers 12 to 23 months of age. Overall, based on available safety data and established routine pharmacovigilance monitoring of clinical trials within the clinical development program, no unexpected safety concerns have been identified in this pediatric population exposed to MenACYW conjugate vaccine. However, the study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in the countries where the trial is taking place.

If the trial is prematurely terminated or suspended, the Sponsor will promptly inform investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigators will promptly inform the participants' parents / guardians and should assure appropriate therapy and follow-up.

10.1.6 Dissemination of Clinical Study Data and Results

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, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

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 vivli.org.

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

Professionals involved in the study or in the product 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 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, IEC/IRB 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 the safety of participants 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 on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- 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 different 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.
- The Sponsor or designee will perform monitoring 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 (Table 1.1) 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 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, or more severe than expected for the participant's condition) eg, leading to IMP discontinuation or modification of dosing, and/or fulfilling a seriousness criterion • 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. • Signs, symptoms, or the clinical sequelae of any medication errors with the IMP

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.

10.2.2 Definition of SAE

The following SAE definition is in compliance with the full definition of an SAE and includes all the key criteria as defined in ICH E2A and ICHD E2D. Some criteria may not apply to all study populations.

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.

10.2.3 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 IMP 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 (IMP) will usually be assessed by the investigator only.
  - For SAEs and non-serious AESIs, relationship to study intervention (IMP) will be assessed by both the investigator and the Sponsor (except for injection site reactions at the site of IMP injection which will be related to IMP by default). Sponsor assessment is entered in the 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 is obliged to 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 first 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) and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- 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.
- For causal relationship assessment, the investigator will also consult the IB and/or Product Information, for marketed products.
- The investigator must review and provide an assessment of causal relationship for each unsolicited AE/SAE and document this in the medical notes. 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 investigators may change their 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: +33 1 60 49 70 70
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: CL-CPV-Receipt@sanofi.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 6.4.

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 < 24 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
CRF and DC intensity scale*	**Grade 1:** Minor reaction when injection site is touched **Grade 2:** Cries or protests when injection site is touched **Grade 3**: 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 DC and the intensity will be transcribed in the CRF. 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 < 24 months

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Body temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of body temperature to ≥°38.0°C (≥ 100.4°F)	Vomiting (emesis): forceful expulsion of the stomach contents through the mouth, associated with coordinated contraction of the abdominal and chest wall musculature. Vomiting does not include spitting up.	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	Eating less than normal	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
CRF and DC intensity scale*	**Grade 1:** ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F	**Grade 1:** 1 episode per 24 hours	**Grade 1:** Less than 1 hour	**Grade 1:** Sleepier than usual or less interested in surroundings	**Grade 1:** Eating less than normal	**Grade 1:** Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	**Grade 2:** From 2 to 5 episodes per 24 hours	**Grade 2:** From 1 to 3 hours	**Grade 2:** Not interested in surroundings or did not wake up for a feed / meal	**Grade 2:** Missed 1 or 2 feeds / meals completely	**Grade 2:** Requiring increased attention
	Grade 3: > 39.5°C **or** > 103.1°F	**Grade 3:** At least 6 episodes per 24 hours or requiring intravenous hydration (fluids administered in the arm or leg)	**Grade 3:** More than 3 hours	**Grade 3:** Sleeping most of the time or difficult to wake up	**Grade 3:** Refuses at least 3 feeds / meals or refuses most feeds / meals	**Grade 3:** Inconsolable (cannot be comforted)

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

Important notes for the accurate assessment of body temperature:

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. Body temperature is also to be measured at the time of any apparent fever. The observed daily body temperature and the route of measurement are to be recorded in the diary card, and the highest body temperature will be recorded by the site in the CRF. The preferred route for this study is axillary.

10.2.5.2 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: No interference with activity.
- Grade 2: Some interference with activity and not requiring therapeutic medical intervention
- Grade 3: Prevents daily activity and requires therapeutic medical intervention

10.3 APPENDIX: MEDICATION ERRORS, MISUSES OR ABUSES OF MEDICINAL PRODUCT

All reports of medication error, misuse or abuse in relation to the IMP with or without an AE must be collected and transmitted to the GPV database following standard processes. The Investigator will assess whether or not the medication error, misuse or abuse event has to be reported together with an AE or SAE.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, “getting high” (euphoria).

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

10.4 APPENDIX: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.4.1 European Union

10.4.1.1 Safety Reporting to the Agency

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

A single Annual Safety Report, aligned with ICH E2F, will include safety information for all IMPs (including the reference compound[s]).

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

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

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 2.3.3, Section 5.5, Section 6.5, Section 7.1.1, Section 7.1.2, 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.

10.6 APPENDIX: COLLECTION, STORAGE, AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.6.1 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of Human Biological Samples (Article 7.1h) of EU Regulation 536/2014

This appendix is provided separately.

10.6.2 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of (Personal) Data (Article 7.1d) of EU Regulation 536/2014

This appendix is provided separately.

10.7 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.

10.8 APPENDIX: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Rationale for the current amendment is located directly before the Table of Contents.

Amendment 1 (27-August-2024)

This amendment (amendment 1) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 1.0 of this protocol is necessary for the following reasons:

- To update the identified and potential risks of clinical significance and risk management based on the review of the Sanofi global pharmacovigilance database (for febrile convulsion) and following a request made by the European Union Pharmacovigilance Risk Assessment Committee (for anaphylaxis)
- Clarification in the statistical and randomization section to specify the randomization stratification by country and specification of the population for the per-protocol definition
- To update the contents of the protocol to reflect that of the current Sanofi protocol template dated 19 March 2024

11 REFERENCES

1. Cornish MJ, Hedrick JA, Gabrielsen AA, Johnson AD, Miriam Pina L, Rehm C, et al. Safety and immunogenicity of an investigational quadrivalent meningococcal tetanus toxoid conjugate vaccine (MenACYW-TT) co-administered with routine pediatric vaccines in infants and toddlers: A Phase II study. Vaccine. 2022;40(10):1421-38.

2. Kirstein J, Pina M, Pan J, Jordanov E, Dhingra MS. Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT) in adults 56 years of age and older: a Phase II randomized study. Hum Vaccin Immunother. 2020;16(6):1299-305.

3. EMA. MenQuadfi Assessment Report 2020 Accessed on 12 March 2025. Available from: https://www.ema.europa.eu/en/documents/assessment-report/menquadfi-epar-public-assessment-report_en.pdf.

4. Baccarini CI, Simon MW, Brandon D, Christensen S, Jordanov E, Dhingra MS. Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine in Healthy Meningococcal-Naïve Children 2-9 Years of Age: A Phase III, Randomized Study. Pediatr Infect Dis J. 2020;39(10):955-60.

5. Mbaeyi SA, Bozio CH, Duffy J, Rubin LG, Hariri S, Stephens DS, et al. Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep. 2020;69(9):1-41.

6. Jafri RZ, Ali A, Messonnier NE, Tevi-Benissan C, Durrheim D, Eskola J, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr. 2013;11(1):17.

7. Oxford Vaccine Group UoO. Meningococcal disease. Vaccine Knowledge Project website. [Available from: http://vk.ovg.ox.ac.uk/meningococcal-disease.

8. ECDC. Factsheet about meningococcal disease.05 March 2025 23 November 2023]. Available from: https://www.ecdc.europa.eu/en/meningococcal-disease/factsheet.

9. MacNeil JR, Bennett N, Farley MM, Harrison LH, Lynfield R, Nichols M, et al. Epidemiology of infant meningococcal disease in the United States, 2006-2012. Pediatrics. 2015;135(2):e305-11.

10. Abu Raya B, Sadarangani M. Meningococcal vaccination in pregnancy. Hum Vaccin Immunother. 2018;14(5):1188-96.

11. Trotter C, Borrow R, Andrews N, Miller E. Seroprevalence of meningococcal serogroup C bactericidal antibody in England and Wales in the pre-vaccination era. Vaccine. 2003;21(11-12):1094-8.

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

13. Yih WK, Weintraub E, Kulldorff M. No risk of Guillain-Barré syndrome found after meningococcal conjugate vaccination in two large cohort studies. Pharmacoepidemiol Drug Saf. 2012;21(12):1359-60.

14. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine--United States, June 2005-September 2006. MMWR Morb Mortal Wkly Rep. 2006;55(41):1120-4.

15. Medicine CtRAEoVIo. Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines. In: Stratton K FA, Rusch E, et al., editor. Adverse Effects of Vaccines: Evidence and Causality. Washington DC: National Academies Press US; 2011.

16. Tseng HF, Sy LS, Ackerson BK, Hechter RC, Tartof SY, Haag M, et al. Safety of Quadrivalent Meningococcal Conjugate Vaccine in 11- to 21-Year-Olds. Pediatrics. 2017;139(1).

17. Nimenrix: Summary of Product Characteristics [Internet]. Available from: https://www.ema.europa.eu/en/documents/product-information/nimenrix-epar-product-information_en.pdf.

18. CDC. Syncope after vaccination - United States, January 2005 - July 2007.2008 Accessed on 05 March 2025; 57(17):457-460. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5717a2.htm.

19. McVernon J, Nolan T, Richmond P, Reynolds G, Nissen M, Lambert SB, et al. A randomized trial to assess safety and immunogenicity of alternative formulations of a quadrivalent meningococcal (A, C, Y, and W-135) tetanus protein conjugate vaccine in toddlers. Pediatr Infect Dis J. 2012;31(1):e15-23.

20. Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004;22(5-6):557-62.

21. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics. 2004;114(6):1708-33.

22. CDC. Kawasaki Syndrome Case Report.2003 Accessed on 05 March 2025. Available from: https://www.cdc.gov/kawasaki/pdf/ks_case_report-fillable.pdf.

23. Phuong LK, Bonetto C, Buttery J, Pernus YB, Chandler R, Goldenthal KL, et al. Kawasaki disease and immunisation: Standardised case definition & guidelines for data collection, analysis. Vaccine. 2016;34(51):6582-96.

24. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

25. Wise RP, Bonhoeffer J, Beeler J, Donato H, Downie P, Matthews D, et al. Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5717-24.

12 SPONSOR SIGNATURE PAGE

Signature Page for VV-CLIN-0647013 v7.0
meq00089-protocol

Approve & eSign	[redacted]

Approve & eSign	[redacted]