NCT04936685

Title Page

Protocol Title:

A Phase IIIb, Open-label, Multi-center Study to Evaluate the Immunogenicity and Safety of a Booster Dose and Describe the Immune Persistence of MenACYW Conjugate Vaccine with 5- and/or 10-year Booster Doses in Children and Adolescents who had been Primed with MenACYW Conjugate Vaccine as Toddlers

Study Code: MEQ00073

Protocol Version Number: 2.0

Amendment Number: 1.0

Compound: MenQuadfi®

Study Phase: IIIb

Short Title:

Study on an Investigational Quadrivalent Meningococcal Conjugate Vaccine (MenACYW Conjugate Vaccine) Administered as a 5- and/or 10-year Booster Dose in Children and Adolescents Vaccinated 5 or 10 Years Earlier as Toddlers

Sponsor Name and Legal Registered Address:

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Manufacturer:

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Regulatory Agency Identifier Number:

EudraCT: 2021-000104-38

Approval Date: 16-Feb-2022

Responsible medical officer (RMO) [and designee(s)], and pharmacovigilance (PV) representative names and contact Information are provided in the Operating Guidelines.

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

Document History

DOCUMENT HISTORY	
Document	**Date**
Amendment 1.0	*16-Feb-2022*
Original Protocol	*08-Feb-2021*

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of Amendment 1.0 is to add a study arm in order to describe the immunogenicity and safety of a booster dose and the persistence of a priming dose of MenACYW conjugate vaccine (MenQuadfi®) in adolescents who had been vaccinated with MenACYW conjugate vaccine approximately 10 years earlier as toddlers as part of the MET51 study. It is also to increase the study duration in the initial study arm to describe the immunogenicity and safety of a second booster dose (as adolescents approximately 5 years after the first booster dose) and the persistence of a first booster dose of MenACYW conjugate vaccine in adolescents who had been primed with MenACYW conjugate vaccine as toddlers as part of the MET51 study and had received a first booster dose as children approximately 5 years after the priming dose.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase IIIb, Open-label, Multi-center Study to Evaluate the Immunogenicity and Safety of a Booster Dose and Describe the Immune Persistence of MenACYW Conjugate Vaccine with 5- and/or 10-year Booster Doses in Children and Adolescents who had been Primed with MenACYW Conjugate Vaccine as Toddlers

Short Title:

Study on an Investigational Quadrivalent Meningococcal Conjugate Vaccine (MenACYW Conjugate Vaccine) Administered as a 5- and/or 10-year Booster Dose in Children and Adolescents Vaccinated 5 or 10 Years Earlier as Toddlers

Rationale:

The purpose of Amendment 1.0 is to add a study arm in order to describe the immunogenicity and safety of a booster dose and the persistence of a priming dose of MenACYW conjugate vaccine (MenQuadfi®) in adolescents who had been vaccinated with MenACYW conjugate vaccine approximately 10 years earlier as toddlers as part of the MET51 study. It is also to increase the study duration in the initial study arm to describe the immunogenicity and safety of a second booster dose (as adolescents approximately 5 years after the first booster dose) and the persistence of a first booster dose of MenACYW conjugate vaccine in adolescents who had been primed with MenACYW conjugate vaccine as toddlers as part of the MET51 study and had received a first booster dose as children approximately 5 years after the priming dose.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To demonstrate the vaccine seroresponse sufficiency of meningococcal serogroups A, C, W, and Y after the administration of a booster dose of MenACYW conjugate vaccine in children who received 1 dose of MenACYW conjugate vaccine approximately 5 years earlier as toddlers (Group 1)	• Vaccine seroresponse[1] against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) assessed at Visit (V)1 (baseline) and at V2 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 1) [1] Seroresponse is defined as the proportions of participants with an hSBA pre-vaccination titer < 1:8 who achieved a post-vaccination titer ≥ 1:16 or participants with a pre-vaccination titer ≥ 1:8 who

	achieved a post-vaccination titer at least 4-fold greater than the pre-vaccination titer
Key Secondary	
Immunogenicity • To describe the antibody persistence of meningococcal serogroups A, C, W, and Y in children who received MenACYW conjugate vaccine approximately 5 years earlier as toddlers (Groups 1 and 2) • To describe the antibody persistence of meningococcal serogroups A, C, W, and Y in adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as toddlers (Group 2) • To describe the antibody persistence of meningococcal serogroups A, C, W, and Y in adolescents who received a booster as children approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1) • To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine in children who received MenACYW conjugate vaccine approximately 5 years earlier as toddlers (Group 1) • To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine in adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as toddlers (Group 2)	***Immunogenicity*** • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and serum bactericidal assay using baby rabbit complement (rSBA) at V1 for Group 1 and Group 2 • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V2 (Group 2) • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V3 (Group 1) • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V1 (baseline) and V2 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V2 and V3 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 2)

• To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine in adolescents who received a booster as children approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1)	• Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V3 and V4 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 1)
• To describe the antibody responses to tetanus toxoid before and 30 days after the administration of each booster dose of MenACYW conjugate vaccine in children (Group 1) and adolescents (Group 2) who received MenACYW conjugate vaccine approximately 5 or 10 years earlier as toddlers and in children who received a booster approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1)	• Antibody concentrations against tetanus toxoid at V1 (baseline) and V2 (30 days after the administration of a 5-year booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody concentrations against tetanus toxoid at V3 and V4 (30 days after administration of the second booster dose of MenACYW conjugate vaccine) (Group 1)
• To describe the antibody responses to meningococcal serogroup C before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine o In children who received MenACYW conjugate vaccine approximately 5 years earlier as meningococcal vaccine naïve toddlers (MET51 Group 1) (Group 1) o In children who received MenACYW conjugate vaccine approximately 5 years earlier as meningococcal C (MenC)-primed toddlers (MET51 Group 3) (Group 1) o In adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as meningococcal vaccine naïve toddlers (MET51 Group 1) (Group 2)	• Antibody concentrations against tetanus toxoid at V2 and V3 (30 days after administration of a 10-year booster dose of MenACYW conjugate vaccine) (Group 2) • Antibody titers[2] against meningococcal serogroup C measured by hSBA and rSBA at V1 (baseline) and V2 (30 days after the administration of a 5-year booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody titers[2] against meningococcal serogroup C measured by hSBA and rSBA at V3 and V4 (30 days after the administration of the second booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody titers[2] against meningococcal serogroup C measured by hSBA and rSBA at V2 and V3 (30 days after the administration of a 10-year booster dose of MenACYW conjugate vaccine) (Group 2)

○ In adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as MenC-primed toddlers (MET51 Group 3) (Group 2) ○ In adolescents who received MenACYW conjugate vaccine booster as children approximately 5 years after receiving the primary dose of MenACYW conjugate vaccine as meningococcal vaccine naïve toddlers (MET51 Group 1) (Group 1) ○ In adolescents who received MenACYW conjugate vaccine booster as children approximately 5 years after receiving the primary dose of MenACYW conjugate vaccine as MenC-primed toddlers (MET51 Group 3) (Group 1)	[2] Results will be expressed as vaccine seroresponse, seorprotection, and GMTs
Safety To describe the safety profile of a booster dose of MenACYW conjugate vaccine: • in children who received MenACYW conjugate vaccine approximately 5 years earlier as toddlers in MET51 (Group 1) • in adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as toddlers in MET51 (Group 2) • in adolescents who received a booster dose as children approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1)	***Safety*** The safety profile will be evaluated within 30 days (+14 days) after vaccination. The following endpoints will be used for the evaluation of safety: • Unsolicited systemic adverse events (AEs) reported within 30 minutes after vaccination • Solicited (prelisted in the participant's diary card [DC] and [electronic] case report book [CRB]) injection site and systemic reactions starting any time from the day of vaccination through 7 days after vaccination • Unsolicited (recorded in a DC) non-serious AEs reported within 30 days after vaccination(s) • Serious adverse events (SAEs) (including adverse events of special interest [AESIs]) reported throughout the study

Overall Design

This is a Phase IIIb, open-label, multi-center study to evaluate the immunogenicity and safety of a booster dose and describe the immune persistence of a priming dose of MenACYW conjugate vaccine in children and adolescents in Finland, Germany, Spain, and Hungary who had been vaccinated with MenACYW conjugate vaccine approximately 5 or 10 years earlier as toddlers as part of the MET51 study, and to describe the immunogenicity and safety of a second booster dose and the persistence of a first booster dose of MenACYW conjugate vaccine in adolescents who had been vaccinated with MenACYW conjugate vaccine approximately 5 years earlier as children.

Participants who were vaccinated with MenACYW conjugate vaccine approximately 5 years earlier at 12 to 23 months of age in study MET51 will be eligible for enrollment in study MEQ00073. Eligible participants will be stratified to 1 of 2 groups based on country and MenC status (primed [Hungary, Spain] or naïve [Finland, Germany]). Participants in Group 1 will receive a first booster dose of MenACYW conjugate vaccine on D01 (V1) (at child age approximately 5 years post priming dose as toddlers in study MET51) and a second booster dose of MenACYW conjugate vaccine at Year 5 of study MEQ00073 (at adolescent age approximately 5 years post booster dose as children in study MEQ00073). Participants in Group 2 will receive a single booster dose of MenACYW conjugate vaccine at Year 5 of study MEQ00073 (approximately 10 years post priming dose as toddlers in study MET51).

All participants will provide blood samples (BL) for antibody persistence and immunogenicity assessments at V1 (pre-vaccination for Group 1 [D01]); participants in Group 1 will also provide a BL at V2 (D31 +14 days), 30 days post-first booster vaccination. Participants in both groups will provide a BL at Year 5 (V3 for Group 1, Visit 2 for Group 2) for antibody persistence and immunogenicity assessments prior to receiving a booster vaccination of MenACYW conjugate vaccine, and another BL 30 days post-booster vaccination (V4 for Group 1, V3 for Group 2).

Solicited AE information will be collected for 7 days after each vaccination; unsolicited AE information will be collected for 30 days (+14 days) after each vaccination. Serious AE information (including AESIs) will be collected throughout the study period.

Type of design	open-label, multi-center and multi-country
Phase	IIIb
Control method	uncontrolled
Study population	Healthy children approximately 6 to 7 years of age at the time of enrollment who were vaccinated with MenACYW conjugate vaccine approximately 5 years earlier as toddlers (12 to 23 months of age) in the MET51 study (Group 1 [naïve] and Group 3 [MenC-primed])
Countries	Finland, Germany, Hungary, Spain
Level and method of blinding	open-label
Study intervention assignment method	randomly selected

Disclosure Statement:

This is an open-label study.

Number of Participants:

All available and eligible participants, who participated in and completed the MET51 study and received a single dose of MenACYW conjugate vaccine as a part of the study, can be enrolled. Participants from MET51 will be invited to participate in MEQ00073, with around 250 participants each in Group 1 and in Group 2 (maximum estimate).

Intervention Groups and Duration:

Participants in Group 1 will receive a first booster dose of MenACYW conjugate vaccine at D01 and a second booster dose of MenACYW conjugate vaccine at Year 5 of study MEQ00073. Participants in Group 2 will receive a single booster dose of MenACYW conjugate vaccine at Year 5 of study MEQ00073.

The duration of each participant's participation will be approximately 5.5 years.

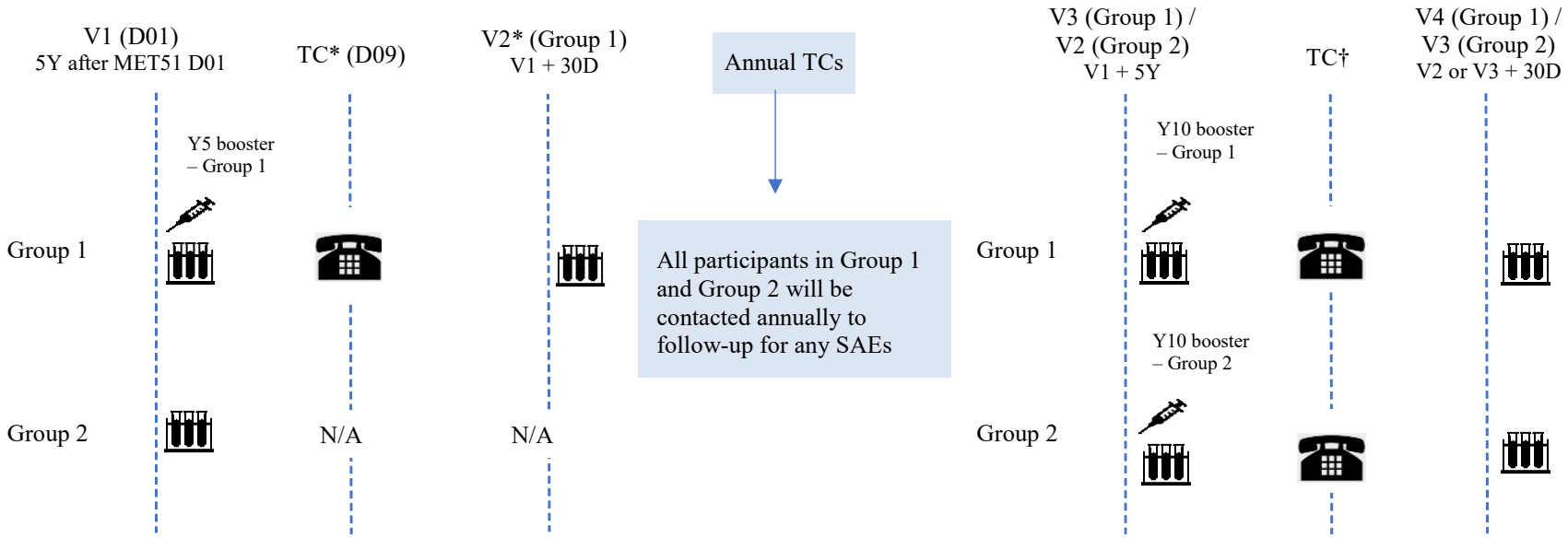
Data Monitoring Committee:

Not applicable

1.2 Schema

The graphical design of study MEQ00073 is presented in Figure 1.1.

Figure 1.1 – Graphical study design



AE: adverse event; D: day; N/A: not applicable; SAE: serious AE; TC: telephone call; V: visit; Y: year

*The TC at D09 and the D31 visit (V2, Group 1) are applicable only to Group 1 participants

† This TC is applicable to both groups, and will be done approximately 8 days after V3 (Group 1) / V2 (Group 2)

1.3 Schedule of Activities (SoA)

Visits procedures are detailed in the Operating Guidelines.

Table 1.1: Schedule of activities, Group 1

Phase IIIb Study, 4 Visits (V), 6 Telephone Calls (TC), 2 Vaccinations, 4 Blood Samples (BLs), 5.5 Years Duration per Participant

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V1)**	**TC1**	**Visit 2 (V2)**	**TC2**	**TC3**	**TC4**	**TC5**	**Visit 3 (V3)**	**TC6**	**Visit 4 (V4)**
Trial timelines (days)		Day 01 (D01)	Day 09 (D09) V1 + 8d	Day 31 (D31) V1 + 30d	Year 1 V1 + 12m	Year 2 V1 + 24m	Year 3 V1 + 36m	Year 4 V1 + 48m	Year 5 V1 + 60m	Year 5 Day 09 V3 + 8d	Year 5 Day 31 V3 + 30d
Time windows (days)		-	+2d	+14d	+14d	+14d	+14d	+14d	+14d	+2d	+14d
Informed consent form (ICF)/Assent form (AF) (As applicable and if required by country regulation, a new AF will be signed by the adolescent aged participant at V3)	*X*	X							X		
Inclusion/exclusion criteria*	*X*	X									
Collection of demographic data	*X*	X									
Collection of medical history	*X*	X									
Collection of vaccination history	*X*	X									
Physical examination		X							X		

Visit/Contact	*Collection of information in the CRF*	Visit 1 (V1)	TC1	Visit 2 (V2)	TC2	TC3	TC4	TC5	Visit 3 (V3)	TC6	Visit 4 (V4)
Trial timelines (days)		Day 01 (D01)	Day 09 (D09) V1 + 8d	Day 31 (D31) V1 + 30d	Year 1 V1 + 12m	Year 2 V1 + 24m	Year 3 V1 + 36m	Year 4 V1 + 48m	Year 5 V1 + 60m	Year 5 Day 09 V3 + 8d	Year 5 Day 31 V3 + 30d
Time windows (days)		-	+2d	+14d	+14d	+14d	+14d	+14d	+14d	+2d	+14d
Urine pregnancy test (if applicable)									X		
Review warnings and precautions and / or contraindications for vaccination	*X*	X							X		
Review of temporary contraindications for blood sampling†	*X*	X		X					X		X
Blood sample (BL), 5 mL‡		BL1		BL2					BL3		BL4
Randomization/stratification of participant number	*X*	X									
Study Vaccination		X							X		
Immediate surveillance post vaccination (30 minutes)	*X*	X							X		
Diary card (DC) provided		DC1		DC for safety					DC2		
Telephone call (TC)			X§		X	X	X	X		X§	
Recording of solicited injection site & systemic reactions	*X*	Day 01 to Day 08							V3 to 7d post-V3		

Visit/Contact	*Collection of information in the CRF*	Visit 1 (V1)	TC1	Visit 2 (V2)	TC2	TC3	TC4	TC5	Visit 3 (V3)	TC6	Visit 4 (V4)
Trial timelines (days)		Day 01 (D01)	Day 09 (D09) V1 + 8d	Day 31 (D31) V1 + 30d	Year 1 V1 + 12m	Year 2 V1 + 24m	Year 3 V1 + 36m	Year 4 V1 + 48m	Year 5 V1 + 60m	Year 5 Day 09 V3 + 8d	Year 5 Day 31 V3 + 30d
Time windows (days)		-	+2d	+14d	+14d	+14d	+14d	+14d	+14d	+2d	+14d
Recording of unsolicited AEs (to be collected up to 30d after vaccination)	*X*			X							X
Reporting of SAEs (including AESIs**)	*X*	To be reported throughout the study period									
DC collected				DC1							DC2
Collection of reportable concomitant medications	*X*	X		X					X		X
Termination record	*X*										X

AE: adverse event; AESI: adverse event of special interest; AF: assent form; AR: adverse reaction; BL: blood sample; CRF: case report form; D, d: day(s); DC: diary card: ICF: informed consent form; m: month(s); mL: milliliter; SAE: serious adverse event; TC: telephone call; V: visit

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

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

‡ Blood samples at V1 (BL1) and V3 (BL3) are to 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 staff will find out whether the participant experienced any SAEs, including AESIs, not yet reported, and are to remind the participant's parent/legally acceptable representative (LAR) to continue using the 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.

** AESIs will be collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

Table 1.2: Schedule of activities, Group 2

Phase IIIb Study, 3 Visits (V), 5 Telephone Calls (TC), 1 Vaccination, 3 Blood Samples (BLs), 5.5 Years Duration per Participant

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V1)**	**TC1**	**TC2**	**TC3**	**TC4**	**Visit 2 (V2)**	**TC5**	**Visit 3 (V3)**
Trial timelines (days)		Day 01 (D01)	Year 1 V1 + 12m	Year 2 V1 + 24m	Year 3 V1 + 36m	Year 4 V1 + 48m	Year 5 V1 + 60m	Year 5 Day 09 V2 + 8d	Year 5 Day 31 V2 + 30d
Time windows (days)		-	+14d	+14d	+14d	+14d	+14d	+2d	+14d
Informed consent form (ICF)/Assent form (AF) (As applicable and if required by country regulation, a new AF will be signed by the adolescent aged participant at V3)	*X*	X					X		
Inclusion/exclusion criteria*	*X*	X							
Collection of demographic data	*X*	X							
Collection of medical history	*X*	X					X		
Collection of vaccination history	*X*	X							
Physical examination		X							
Urine pregnancy test (if applicable)							X		
Review warnings and precautions and / or contraindications for vaccination	*X*						X		

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V1)**	**TC1**	**TC2**	**TC3**	**TC4**	**Visit 2 (V2)**	**TC5**	**Visit 3 (V3)**
Trial timelines (days)		Day 01 (D01)	Year 1 V1 + 12m	Year 2 V1 + 24m	Year 3 V1 + 36m	Year 4 V1 + 48m	Year 5 V1 + 60m	Year 5 Day 09 V2 + 8d	Year 5 Day 31 V2 + 30d
Time windows (days)		-	+14d	+14d	+14d	+14d	+14d	+2d	+14d
Review of temporary contraindications for blood sampling†	*X*	X					X		X
Blood sample (BL), 5 mL		BL1					BL2‡		BL3
Randomization/stratification of participant number	X	X							
Study Vaccination							X		
Immediate surveillance post vaccination (30 minutes)	*X*						X		
Diary card (DC) provided		DC for safety					DC1		
Telephone call (TC)			X	X	X	X		X§	
Recording of solicited injection site & systemic reactions	*X*						V2 to 7d post-V2		
Recording of unsolicited AEs (to be collected up to 30d after vaccination)	*X*								X
Reporting of SAEs (including AESIs**)	*X*		To be reported throughout the study period						
DC collected									DC1

Visit/Contact	*Collection of information in the CRF*	Visit 1 (V1)	TC1	TC2	TC3	TC4	Visit 2 (V2)	TC5	Visit 3 (V3)
Trial timelines (days)		Day 01 (D01)	Year 1 V1 + 12m	Year 2 V1 + 24m	Year 3 V1 + 36m	Year 4 V1 + 48m	Year 5 V1 + 60m	Year 5 Day 09 V2 + 8d	Year 5 Day 31 V2 + 30d
Time windows (days)		-	+14d	+14d	+14d	+14d	+14d	+2d	+14d
Collection of reportable concomitant medications	*X*	X					X		X
Termination record	*X*								X

AE: adverse event; AESI: adverse event of special interest; AF: assent form; AR: adverse reaction; BL: blood sample; CRF: case report form; D, d: day(s); DC: diary card: ICF: informed consent form; m: month(s); mL: milliliter; SAE: serious adverse event; TC: telephone call; V: visit

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

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

‡ Blood sample at V2 (BL2) is to 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 staff will find out whether the participant experienced any SAEs, including AESIs, not yet reported, and are to remind the participant's parent/legally acceptable representative (LAR) to continue using the 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.

** AESIs will be collected throughout the trial as SAEs to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality. Before the first booster vaccination at V2, only SAEs related to study procedures are to be collected for Group 2.

2 Introduction

The MenACYW conjugate vaccine (MenQuadfi®) was designed for the immunization of individuals of all ages (children as young as 6 weeks of age, adolescents, and adults including those 56 years of age and older) 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.

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

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

2.1 Study Rationale

The MEQ00073 study will assess the immunogenicity and safety of a booster dose in children who had been vaccinated with MenACYW conjugate vaccine approximately 5 years earlier as toddlers as part of the MET51 study; it will describe the persistence of a priming dose in children and adolescents who had been vaccinated with MenACYW conjugate vaccine approximately 5 years or 10 years earlier as toddlers as part of the MET51 study, the immunogenicity and safety of a booster dose in adolescents who had been primed with MenACYW conjugate vaccine as toddlers as part of the MET51 study, and the immunogenicity and safety of a second booster dose in adolescents approximately 5 years after a first booster dose as children approximately 5 years after the priming dose as toddlers.

MET51

MET51, entitled “Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Toddlers 12 to 23 Months of Age”, was a Phase III modified, double blind randomized, parallel group, active-controlled, multi-center study conducted in Spain, Hungary, Finland, and Germany. This study focused on evaluating the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine compared to those of the licensed quadrivalent meningococcal serogroups A, C, W, and Y tetanus toxoid conjugate vaccine (Nimenrix®) among toddlers 12 to 23 months of age in the EU who were either meningococcal vaccine naïve (Finland and Germany) or had received meningococcal C (MenC) vaccination (Spain and Hungary) during infancy.

A total of 918 participants 12 to 23 months of age were enrolled and randomly allocated to one of the following 4 groups:

Meningococcal vaccine-naïve participants were randomized in a 1:1 ratio to the following 2 groups:

- Group 1: MenACYW conjugate vaccine (306 participants)
- Group 2: Nimenrix vaccine (306 participants)

MenC-primed participants were randomized in a 2:1 ratio to the following 2 groups:

- Group 3: MenACYW conjugate vaccine (203 participants)
- Group 4: Nimenrix vaccine (103 participants)

All meningococcal vaccine-naïve participants (Groups 1 and 2) were enrolled in Finland (356 [38.8%] participants) and Germany (256 [27.9%] participants), and all MenC-primed participants (Groups 3 and 4) were enrolled in Hungary (145 [15.8%] participants) and Spain (161 [17.5%] participants).

In MenC-primed toddlers vaccinated with MenACYW conjugate vaccine (Group 3), 151 (74.4%) and 52 (25.6%) participants were MenC-TT- and MenC-CRM-primed, respectively. In MenC-primed toddlers vaccinated with the Nimenrix vaccine (Group 4), 77 (74.8%) and 26 (25.2%) participants were MenC-TT- and MenC-CRM-primed, respectively.

Overall, vaccination with MenACYW conjugate vaccine among toddlers 12 to 23 months of age was found to be well-tolerated, with no safety concerns identified, no immediate hypersensitivity reactions, no discontinuations due to a serious adverse event (SAE) or other adverse event (AE), and no related SAEs.

The 2 co-primary objectives were met:

- Non-inferiority of immune response, based on percentage of participants achieving a post-vaccination titer ≥ 1:8 (seroprotection) at Day (D)30 regardless of their meningococcal vaccine background, was demonstrated for MenACYW conjugate vaccine versus Nimenrix vaccine for all serogroups
- Non-inferiority of immune response, based on percentage of participants achieving a post-vaccination titer ≥ 1:8 (seroprotection) at D30 in meningococcal vaccine-naïve toddlers, was demonstrated for MenACYW conjugate vaccine versus Nimenrix vaccine for all serogroups

<u>As well as the secondary objectives and observational objectives:</u>

At D30, the percentage of participants with a seroresponse to serogroup C, based on serum bactericidal assay using human complement (hSBA), was higher in MenACYW conjugate vaccine recipients than in Nimenrix vaccine recipients. For the other serogroups, percentages were similar between MenACYW conjugate vaccine recipients and Nimenrix vaccine recipients.

Antibody Responses (hSBA Geometric Mean Titers [GMTs]) at D30

Toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy

The geometric mean titer ratios (GMTRs) (stratified on priming vaccination background) were 7.59, 1.32, and 1.28 for serogroups C, W, and Y, respectively, with the lower bound of the 95% confidence interval (CI) greater than 1.0; and the GMTR (stratified on priming vaccination background) was 0.819 for serogroup A, with the upper bound of the 95% CI lower than 1.0.

Meningococcal vaccine-naïve toddlers

The GMTRs were 1.03 and 1.18 (with the lower bound of the 95% CI below 1.0) for serogroups A and Y, respectively, and 16.5 and 1.34 (with the lower bound of the 95% CI greater than 1.0) for serogroups C and W, respectively.

Table 2.1 shows a comparison of the bactericidal antibody responses to MenACYW conjugate vaccine and Nimenrix vaccine 30 days after the vaccination of meningococcal vaccine naïve subjects only or combined (naïve + MenC-primed) subjects 12 through 23 months of age.

Table 2.1: Comparison of bactericidal antibody responses to MenACYW conjugate vaccine and Nimenrix Vaccine Reported in MET51

Endpoint by Serogroup	MenACYW (95% CI) Naïve	Nimenrix vaccine (95% CI) Naïve	MenACYW (95% CI) Combined (Naïve + MenC Primed)	Nimenrix vaccine (95% CI) Combined (Naïve + MenC Primed)
A	**N=293**	**N=295**	**N=490**	**N=393-394**
% ≥ 1:8 (Seroprotection)**	90.8 (86.9; 93.8)	89.5 (85.4; 92.7)	90.4 (87.4; 92.9)	91.6 (88.4; 94.2)
% Seroresponse	76.8 (71.5; 81.5)	72.5 (67.1; 77.6)	76.5 (72.5; 80.2)	77.1 (72.6; 81.2)
hSBA GMT	28.7 (25.2; 32.6)	28.0 (24.4; 32.1)	29.9 (26.9; 33.2)	34.5 (30.5; 39.0)
C	**N=293**	**N=295**	**N=489**	**N=393-394**
% ≥ 1:8 (Seroprotection)**	99.3 (97.6; 99.9)	81.4 (76.4; 85.6)	99.2 (97.9; 99.8)	85.5 (81.7; 88.9)
% Seroresponse	98.3 (96.1; 99.4)	71.5 (66.0; 76.6)	97.1 (95.2; 98.4)	77.4 (72.9; 81.4)
hSBA GMT	436 (380; 500)	26.4 (22.5; 31.0)	880 (748; 1035)	77.1 (60.7; 98.0)

Endpoint by Serogroup	MenACYW (95% CI) Naïve	Nimenrix vaccine (95% CI) Naïve	MenACYW (95% CI) Combined (Naïve + MenC Primed)	Nimenrix vaccine (95% CI) Combined (Naïve + MenC Primed)
W	**N=293**	**N=296**	**N=489**	**N=393-394**
% ≥ 1:8 (Seroprotection)**	83.6 (78.9; 87.7)	83.4 (78.7; 87.5)	84.9 (81.4; 87.9)	84.0 (80.0; 87.5)
% Seroresponse	67.6 (61.9; 72.9)	66.6 (60.9; 71.9)	70.8 (66.5; 74.8)	68.4 (63.6; 73.0)
hSBA GMT	22.0 (18.9; 25.5)	16.4 (14.4; 18.6)	24.4 (21.8; 27.5)	17.7 (15.8; 19.8)
Y	**N=293**	**N=296**	**N=488-490**	**N=394-395**
% ≥ 1:8 (Seroprotection)**	93.2 (89.7; 95.8)	91.6 (87.8; 94.5)	94.3 (91.8; 96.2)	91.6 (88.5; 94.2)
% Seroresponse	81.9 (77.0; 86.1)	79.1 (74.0; 83.5)	84.8 (81.3; 87.9)	78.9 (74.6; 82.9)
hSBA GMT	38.0 (33.0; 43.9)	32.2 (28.0; 37.0)	41.7 (37.5; 46.5)	31.9 (28.4; 36.0)

N: number of subjects in the per-protocol analysis set
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met

Toddlers who received monovalent MenC vaccination during infancy

The GMTRs were 0.496 (with the upper bound of the 95% CI lower than 1.0) for serogroup A, 1.34 and 1.29 (with the lower bound of the 95% CI below 1.0) for serogroups C and W, respectively, and 1.53 (with the lower bound of the 95% CI greater than 1.0) for serogroup Y.

Response in toddlers previously vaccinated with MenC conjugate vaccines in their first year of life

The majority of monovalent MenC-primed toddlers (12 to 23 months of age) in study MET51 (NCT02955797) had hSBA titers ≥ 1:8 in the MenQuadfi group (N=198) (≥ 86.7%) and in MenACWY-TT group (N=99) (≥ 85.7%) at D30 post-vaccination. These toddlers received during their infancy MenC-TT or MenC-CRM vaccines. Post-vaccination seroprotection rates were comparable between MenQuadfi and MenACWY-TT for all serogroups regardless of the priming background.

In MenC-CRM-primed toddlers, the GMTs for serogroup A were lower in the MenQuadfi group (n=49) than in the MenACWY-TT group (n=25) (12.0 [8.23; 17.5] vs 42.2 [25.9; 68.8]). After administration of MenQuadfi, seroprotection rates (hSBA titers ≥ 1:8) for toddlers primed with MenC-CRM were lower but still comparable for serogroups A, Y and W compared with those in the MenACWY-TT group (A: 68.8% [53.7; 81.3] vs 96.0% [79.6; 99.9]; Y: 95.8% [85.7; 99.5] vs

80.0% [59.3; 93.2]; W: 68.1% [52.9; 80.9] vs 79.2% [57.8; 92.9]). The rates for serogroup C were comparable in both groups (95.7% [85.5; 99.5] vs 92.0% [74.0; 99.0]). The clinical relevance of these results is unknown. This aspect might be considered for individuals at high risk for MenA infection who received MenC-CRM vaccine in their first year of life.

Antibody Responses (serum bactericidal assay using baby rabbit complement [rSBA] GMTs and Titers ≥ 1:8) at D30

Toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy

At D30, meningococcal rSBA GMTs were lower in MenACYW recipients than in Nimenrix vaccine recipients for serogroup A (1382 and 4882, respectively), and higher in MenACYW recipients than in Nimenrix vaccine recipients for serogroup C (2150 and 686, respectively).

Thirty days after vaccination, the percentages of participants with rSBA antibody titers ≥ 1:8 were high and comparable between MenACYW and Nimenrix vaccine recipients ranging from 97.3% to 100.0% for all serogroups.

Other relevant Phase II and Phase III studies that concern the toddler populations are discussed below.

MET62

MET62 entitled, "Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered as a Booster Dose in Children Vaccinated 3 Years Earlier as Toddlers", was a Phase III, open-label, multi-center trial to describe the immune persistence of the priming dose and describe the immunogenicity and safety of a booster dose of MenACYW conjugate vaccine in children 4 to 5 years of age in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix vaccine as part of the MET54 clinical trial. MET54 was a Phase II randomized, open-label, active-controlled study conducted to describe the safety and immunogenicity of MenACYW conjugate vaccine compared to Nimenrix vaccine in meningococcal vaccine naïve toddlers 12 to 23 months of age. A total of 188 participants were enrolled.

A total of 91 participants were enrolled in the MET62 clinical trial.

- Group 1 (MenACYW primed – MenACYW booster): 42
- Group 2 (Nimenrix vaccine primed – MenACYW booster): 49

Vaccination with MenACYW conjugate vaccine given as a booster in children vaccinated 3 years earlier with either MenACYW conjugate vaccine or Nimenrix vaccine was found to be well-tolerated with no safety concerns identified. The safety profile of a booster dose of MenACYW conjugate vaccine in MenACYW conjugate vaccine-primed participants was comparable to that in Nimenrix vaccine-primed participants. No SAEs, adverse events of special interest (AESIs) or cases of death were reported during the study.

Antibody Responses to Meningococcal Serogroups A, C, W, and Y at Baseline (D0) and D30 Measured by rSBA

rSBA GMTs

Meningococcal rSBA GMTs were higher at D30 than at baseline for all 4 serogroups in both study groups. The rSBA GMT immune response in Group 1 was comparable for serogroups A, W, and Y (4240, 16103, and 5499, respectively) and higher for serogroup C (8629) compared to those in Group 2 (5702, 4871, 19793, and 7814, respectively for serogroups A, C, W, and Y).

Proportion of Participants with rSBA Antibody Titers ≥ 1:8 and ≥ 1:128 30 Days After Vaccination

All participants in both study groups had rSBA titers ≥ 1:8 at D30. For all serogroups, the percentages of participants were 100% for both study groups.

All participants in both study groups had rSBA titers ≥ 1:128 at D30. For all serogroups, the percentages of participants were 100% for both study groups.

Fold Rise in rSBA Antibody Titers

Most participants in both study groups had a ≥ 4-fold rise in rSBA antibody titers at D30. The percentages of participants with a ≥ 4-fold rise in rSBA antibody titers 30 days after vaccination in Group 1 (92.3%, 94.9%, 100%, and 100%, respectively for serogroups A, C, W, and Y) were comparable to those in Group 2 (81.8%, 97.7%, 100%, and 100%, respectively for serogroups A, C, W, and Y).

rSBA Vaccine Seroresponse

Most participants in both study groups demonstrated an rSBA vaccine seroresponse at D30. The percentages of participants with an hSBA vaccine seroresponse were comparable in Group 1 (ranging from 92.3% to 100%) to those in Group 2 (ranging from 81.8% to 100%).

Overall, the MenACYW conjugate vaccine had comparable immune response in both study groups across all 4 serogroups.

This provides evidence that the MenACYW conjugate vaccine can boost MenACYW conjugate vaccine-primed children as well as Nimenrix vaccine-primed children.

In addition to the studies MET51 and MET62 described above, the relevant Phase III (MET35) study in children population (2 to 9 years of age) is discussed in the Investigator's Brochure (IB) Section 5.

Current Study MEQ00073

The MET51 study enrollment period was February 2017 to September 2017. There is now the opportunity to generate persistence and booster data approximately 5 and 10 years after vaccination with MenACYW conjugate vaccine in toddlers. Therefore, this MEQ00073 study will provide longer persistence data than in the MET62 study, with a larger sample size. It also is intended to further confirm that the MenACYW conjugate vaccine can boost MenACYW conjugate vaccine-primed children and adolescents. The boostability of MenACYW conjugate vaccine in children who were MenACYW conjugate vaccine-primed as toddlers will be determined by sufficiency of the seroresponse measured using hSBA 30 days post-booster in

Group 1. With this amendment, the boostability of MenACYW conjugate vaccine will also be described in adolescents primed with MenACYW conjugate vaccine approximately 10 years earlier as toddlers (Group 2) and in adolescents boosted as children approximately 5 years earlier (after priming at toddler age [Group 1]). The persistence of the immune response against meningococcal serogroups A, C, W, and Y in adolescents approximately 10 years after the primary vaccination as toddlers (Group 2) and in adolescents approximately 5 years after a booster dose administered as children (approximately 5 years after priming at toddler age [Group 1]) will be described.

MenC titers will also be described according to the priming status in infancy before receiving the toddler dose in MET51 study (meningococcal vaccine naïve or MenC-primed).

2.2 Background

IMD is a serious illness caused by the bacterium *Neisseria meningitidis* (*N meningitidis*), a Gram-negative diplococcus found exclusively in humans. It is associated with high morbidity and mortality. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). IMD usually results in septicemia (~35%–40% of cases), meningitis (~50% of cases), or both. Bacteremic pneumonia is less common (~9% of cases). At least 12 distinct meningococcal serogroups have been classified based on the immunochemistry of the capsular polysaccharides (PS). Some strains are more likely than others to cause infection (1) (2) (3). Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (2) (3) (4). Serogroup B is responsible for endemic disease and some outbreaks, while serogroup C is responsible for large outbreaks (5). Serogroup A is the main cause of epidemics in the world, and is especially dominant in Africa and Asia but is only minor in Europe. Serogroup W has been seen in Africa, as well as in the United Kingdom (UK) in residents who participated in the Hajj pilgrimage to the Kingdom of Saudi Arabia (4) (6) (7) and more recently in Chile (8), Turkey (9) (10), China (11) (12), Argentina (13), and Brazil (14) (15) and in other parts of the world. An increasing trend of the notification rate of serogroup W is seen in Europe. Serogroup X causes substantial meningococcal disease in parts of Africa but rarely causes disease in other parts of the world (2) (16). Serogroup Y has not been associated with outbreaks, but its frequency as a cause of sporadic cases has gradually increased in the US and more recently in Canada and Europe (17) (18) (19). This serogroup is commonly associated with meningococcal pneumonia, particularly in older adults > 65 years of age (20).

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

In Europe, the European Center for Disease Prevention and Control (ECDC) annually publishes an epidemiological report on IMD, based on data retrieved from the European Surveillance System (TESSy) which is used to collect, analyze, and disseminate data on communicable diseases. The last report has been published in April 2019, based on 2017 data. As per this report, in 2017, the overall notification rate of IMD in EU/European Economic Area (EEA) countries was 0.6 per 100 000 population, similar to the notification rate for previous years. IMD remains rare in EU/EEA countries, but is a severe and life-threatening disease. The greatest burden is in infants and young children: case fatality is relatively high and up to one fifth of all survivors suffer from

long-term sequelae (21). There was a notification rate of 8.2 confirmed cases per 100 000 population in children under 1 year of age, and 2.5 confirmed cases per 100 000 population in children 1 to 4 years of age. There was a second peak in people 15 to 24 years of age, with a rate of 1.0 per 100 000. Infants were the most affected age group in the majority of Member States, with county-specific rates varying from 0–36.2 cases per 100 000.

In 2017, 3221 confirmed cases of IMD were reported in 30 EU/EEA countries. Four countries (France, Germany, Spain, and the UK) accounted for 58% of all confirmed cases. In the countries involved in the MEQ00073 study, the incidence per 100 000 was 0.3 in Finland and in Germany, 0.4 in Hungary and 0.6 in Spain.

The majority of IMD cases belonged to serogroup B (51%), followed by W and C (17% and 16%, respectively). Serogroup B caused the highest proportion of cases in all age groups below 65 years of age and accounted for 70% of IMD in children under the age of 5 years, but only 24% of cases concerned adults 65 years of age and above. Serogroup C was most prominent in adults 25 to 49 years of age, accounting for 27% of cases in this age group. Serogroups W and Y were most prominent in adults 65 years of age and above, causing 30% and 26% of IMD cases, respectively, in this age group. Notifications of serogroup B decreased from 0.42 cases per 100 000 in 2013 to 0.30 cases in 2017). The decrease was most pronounced in children, where rates diminished from 10.4 to 5.4 per 100 000 in children < 1 year of age, and from 2.6 to 1.7 per 100 000 in children 1 to 4 years of age, from 2013 to 2017. A 3-fold increase of serogroup W was observed between 2013 and 2017 (from 0.03 to 0.10 per 100 000). The increase was most pronounced among young children and adults above 50 years of age. The incidence per 100 000 in 2013 and 2017 were 0.6 and 1.2 in children < 1 year of age, 0.09 and 0.31 in children 1 to 4 years of age, 0.03 and 0.10 in adults 50 to 64 years of age and 0.06 and 0.20 in adults 65 years of age or above, respectively. The notification rates of serogroups C and Y have fluctuated between 0.08–0.10 and 0.05–0.07 per 100 000 respectively during the last 5 years.

In Europe, the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 19 years of age group. The highest incidence rate in Europe is caused by serogroup B, followed by C and W (21). The highest proportion of meningococcal cases was due to serogroup B in the population under 5 years of age. The highest proportion of serogroup C cases was observed in the population 25 to 44 years of age while the proportion of serogroup Y cases was highest in the population 65 years of age and above.

In this context of increasing trends for serogroups W and Y, several EU countries have introduced or consider to introduce the quadrivalent conjugate vaccine MenACYW into their routine vaccination schedules, predominantly as booster doses for adolescents, but also in some countries targeting toddlers, switching from MenC to MenACYW vaccination. The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, Y, and W in all age groups: children as young as 6 weeks of age, adolescents, and adults including those 56 years of age and older.

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 the MenACYW conjugate vaccine may be found in the IB, Participant Information Leaflet, Package Insert, or Summary of Product Characteristics (SmPC) (22).

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.2.

Table 2.2: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: MenACYW conjugate vaccine		
Anaphylaxis	Known important risk occurring at a low frequency (very rare) based on what would be common for any vaccine. One case of anaphylaxis was reported 10 minutes after receiving the second dose of MenQuadfi given alone in study MET52. While temporal relationship was consistent with causal association to MenACYW conjugate vaccine and anaphylaxis has been reported with association to immunization in general, causality was assessed as related.	Observation period after vaccination for early detection and treatment. Exclusion criteria: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Guillain-Barré syndrome (GBS)	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 (23) (24) (25). A review by the Institute of Medicine found inadequate evidence to accept or reject a causal relationship between tetanus toxoid-containing vaccines and GBS (26). No cases with MenACYW conjugate vaccine in the completed studies.	Exclusion criteria: Personal history of GBS

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Bell's palsy Refer to IB Section 6 for more information regarding potential risks	Important potential risk-based on post-marketing experience for other quadrivalent meningococcal conjugate vaccines occurring at a low frequency (very rare). 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 (27). 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
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 (28). Cases of vasovagal-like response (eg, dizziness) or syncope have been observed infrequently in adolescent or young adult study participants within 30 minutes of vaccination with MenACYW conjugate vaccine.	Observation period after vaccination for early detection and treatment. Procedures should be in place to prevent falling injury and manage syncopal reactions.

2.3.2 Benefits from Study Participation

There might be no direct benefit from receiving MenACYW conjugate vaccine. However, based on the data from previous studies, evaluation of the immunogenicity profile of MenACYW conjugate vaccine in different age groups shows that the majority of subjects develop seroprotective levels of antibodies after vaccination. Participants may experience additional protection after administration of a booster dose(s) approximately 5 and/or 10 years after primary vaccination in the MET51 study. The safety evaluation indicates that the vaccine is well-tolerated, and no safety issues have been detected to date. In all, the data support the further evaluation of MenACYW conjugate vaccine in humans.

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

2.3.3 COVID-19 Risk Assessment

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

Risk Mitigation:

- Not start the study until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local Authorities.
- Continued risk assessment by the Investigator and Sponsor before deciding to start the study.
- Reduce the public exposure while ambulatory when possible.
- In order to limit the participant visits to the hospital, visits (blood draw, physical examination, safety assessments) may be conducted at the site (site visit) or at the participant's home (home visit) except for V1 (Group 1 and Group 2), V3 (Group 1), and V2 (Group 2) that must be conducted at the investigational site.

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
Primary	
• To demonstrate the vaccine seroresponse sufficiency of meningococcal serogroups A, C, W, and Y after the administration of a booster dose of MenACYW conjugate vaccine in children who received 1 dose of MenACYW conjugate vaccine approximately 5 years earlier as toddlers (Group 1)	• Vaccine seroresponse[1] against meningococcal serogroups A, C, W, and Y measured by hSBA assessed at Visit (V)1 (baseline) and at V2 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 1) [1] Seroresponse is defined as the proportions of participants with an hSBA pre-vaccination titer < 1:8 who achieved a post-vaccination titer ≥ 1:16 or participants with a pre-vaccination titer ≥ 1:8 who achieved a post-vaccination titer at least 4-fold greater than the pre-vaccination titer

Objectives	Endpoints
Secondary	
Immunogenicity • To describe the antibody persistence of meningococcal serogroups A, C, W, and Y in children who received MenACYW conjugate vaccine approximately 5 years earlier as toddlers (Groups 1 and 2) • To describe the antibody persistence of meningococcal serogroups A, C, W, and Y in adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as toddlers (Group 2) • To describe the antibody persistence of meningococcal serogroups A, C, W, and Y in adolescents who received a booster as children approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1) • To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine in children who received MenACYW conjugate vaccine approximately 5 years earlier as toddlers (Group 1) • To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine in adolescents who received MenACYW	***Immunogenicity*** • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V1 (baseline) for Group 1 and Group 2 • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V2 (Group 2) • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by SBA and rSBA at V3 (Group 1) • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V1 (baseline) and V2 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V2 and V3 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 2) • Antibody titers[2] against meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA at V3 and V4 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody concentrations against tetanus toxoid at V1 (baseline) and V2 (30 days after the administration of a 5-year booster dose of MenACYW conjugate vaccine) (Group 1)

Objectives	Endpoints
conjugate vaccine approximately 10 years earlier as toddlers (Group 2) • To describe the antibody responses to meningococcal serogroups A, C, W, and Y before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine in adolescents who received a booster as children approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1) • To describe the antibody responses to tetanus toxoid before and 30 days after the administration of each booster dose of MenACYW conjugate vaccine in children (Group 1) and adolescents (Group 2) who received MenACYW conjugate vaccine approximately 5 or 10 years earlier as toddlers and in children who received a booster approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1) • To describe the antibody responses to meningococcal serogroup C before and 30 days after the administration of a booster dose of MenACYW conjugate vaccine o In children who received MenACYW conjugate vaccine approximately 5 years earlier as meningococcal vaccine naïve toddlers (MET51 Group 1) (Group 1) o In children who received MenACYW conjugate vaccine approximately 5 years earlier as	• Antibody concentrations against tetanus toxoid at V3 and V4 (30 days after administration of the second booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody concentrations against tetanus toxoid at V2 and V3 (30 days after administration of a 10-year booster dose of MenACYW conjugate vaccine) (Group 2) • Antibody titers[2] against meningococcal serogroup C measured by hSBA and rSBA at V1 (baseline) and V2 (30 days after the administration of a 5-year booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody titers[2] against meningococcal serogroup C measured by hSBA and rSBA at V3 and V4 (30 days after the administration of the second booster dose of MenACYW conjugate vaccine) (Group 1) • Antibody titers[2] against meningococcal serogroup C measured by hSBA and rSBA at V2 and V3 (30 days after the administration of a 10-year booster dose of MenACYW conjugate vaccine) (Group 2) [2] Results will be expressed as vaccine seroresponse, seorprotection, and GMTs

Objectives	Endpoints
meningococcal C (MenC)-primed toddlers (MET51 Group 3) (Group 1) o In adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as meningococcal vaccine naïve toddlers (MET51 Group 1) (Group 2) o In adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as MenC-primed toddlers (MET51 Group 3) (Group 2) o In adolescents who received MenACYW conjugate vaccine booster as children approximately 5 years after receiving the primary dose of MenACYW conjugate vaccine as meningococcal vaccine naïve toddlers (MET51 Group 1) (Group 1) o In adolescents who received MenACYW conjugate vaccine booster as children approximately 5 years after receiving the primary dose of MenACYW conjugate vaccine as MenC-primed toddlers (MET51 Group 3) (Group 1)	
Safety To describe the safety profile of a booster dose of MenACYW conjugate vaccine: • in children who received MenACYW conjugate vaccine approximately	***Safety*** The safety profile will be evaluated within 30 days (+14 days) after vaccination. The following endpoints will be used for the evaluation of safety:

Objectives	Endpoints
5 years earlier as toddlers in MET51 (Group 1) • in adolescents who received MenACYW conjugate vaccine approximately 10 years earlier as toddlers in MET51 (Group 2) • in adolescents who received a booster dose as children approximately 5 years after the primary dose of MenACYW conjugate vaccine as toddlers (Group 1)	• Unsolicited systemic AEs reported within 30 minutes after vaccination. • Solicited (prelisted in the participant's diary card [DC] and [electronic] case report book [CRB]) injection site and systemic reactions starting any time from the day of vaccination through 7 days after vaccination. • Unsolicited (recorded in a DC) non-serious AEs reported within 30 days after vaccination(s). • SAEs (including AESIs) reported throughout the study

4 Study Design

4.1 Overall Design

This is a Phase IIIb, open-label, multi-center study to evaluate the immunogenicity and safety of a booster dose and describe the immune persistence of a priming dose of MenACYW conjugate vaccine in children and adolescents in Finland, Germany, Spain, and Hungary who had been vaccinated with MenACYW conjugate vaccine approximately 5 or 10 years earlier as toddlers as part of the MET51 study, and to describe the immunogenicity and safety of a second booster dose and the persistence of a first booster dose of MenACYW conjugate vaccine in adolescents who had been vaccinated with MenACYW conjugate vaccine approximately 5 years earlier as children.

Participants who were vaccinated with MenACYW conjugate vaccine approximately 5 years earlier at 12 to 23 months of age in study MET51 will be eligible for enrollment in study MEQ00073. Eligible participants will be stratified to 1 of 2 groups based on country and MenC status (primed [Hungary, Spain] or naïve [Finland, Germany]). Participants in Group 1 will receive a first booster dose of MenACYW conjugate vaccine on D01 (V1) (at child age approximately 5 years post priming dose as toddlers in study MET51) and a second booster dose of MenACYW conjugate vaccine at Year 5 of study MEQ00073 (at adolescent age approximately 5 years post booster dose as children in study MEQ00073). Participants in Group 2 will receive a single booster dose of MenACYW conjugate vaccine at Year 5 of study MEQ00073 (approximately 10 years post priming dose as toddlers in study MET51).

All participants will provide blood samples (BL) for antibody persistence and immunogenicity assessments at V1 (pre-vaccination for Group 1 [D01]); participants in Group 1 will also provide a

BL at V2 (D31 +14 days), 30 days post-first booster vaccination. Participants in both groups will provide a BL at Year 5 (V3 for Group 1, V2 for Group 2) for antibody persistence and immunogenicity assessments prior to receiving a booster vaccination of MenACYW conjugate vaccine, and another BL 30 days post-booster vaccination (V4 for Group 1, V3 for Group 2).

Solicited AE information will be collected for 7 days after each vaccination; unsolicited AE information will be collected for 30 days (+14 days) after each vaccination. Serious AE information (including AESIs) will be collected throughout the study period, however for Group 2 before the first study intervention is administered at V2, only SAEs related to study procedures are to be collected.

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	open-label, multi-center and multi-country
Phase	IIIb
Control method	uncontrolled
Study population	Healthy children approximately 6 to 7 years of age at the time of enrollment who were vaccinated with MenACYW conjugate vaccine approximately 5 years earlier as toddlers (12 to 23 months of age) in the MET51 study (Group 1 [naïve] and Group 3 [MenC-primed])
Level and method of blinding	open-label
Study intervention assignment method	randomly selected
Number of participants	All available and eligible participants, who participated in and completed the MET51 study and received a single dose of MenACYW conjugate vaccine as a part of the study, can be enrolled. The total maximum number of children expected for enrollment is around 500 participants (MET51 participants who received MenACYW conjugate vaccine approximately 5 years earlier), with approximately 250 participants each in Group 1 and Group 2

Intervention groups	Participants in Group 1 will receive a dose of MenACYW conjugate vaccine at D01 (V1) and a dose of MenACYW conjugate vaccine at Year 5 (V3). Participants in Group 2 will receive a single dose of MenACYW conjugate vaccine at Year 5 (V2)
Total duration of study participation	The duration of each participant's participation will be approximately 5.5 years
Countries	Finland, Germany, Hungary, Spain
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

4.2 Scientific Rationale for Study Design

The clinical development of MenACYW conjugate vaccine has started in 2006 with the objective to provide protection against 4 serogroups (A, C, Y, and W) that cause IMD, in all population age groups, including infant as young as 6 weeks of age and including adults 56 years of age and older.

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

The clinical studies supporting the first licensure were designed to demonstrate the ability of MenACYW conjugate vaccine to safely elicit a robust immune response. Studies were conducted to demonstrate efficacy through the non-inferiority of MenACYW conjugate vaccine compared to licensed meningococcal standard of care vaccines. The potential impact of concomitant administration of MenACYW conjugate vaccine with routine licensed vaccines in toddlers and adolescents and the suitability of MenACYW conjugate vaccine administered as a booster dose were assessed as well.

At the time of initial licensure, limited data were available regarding booster vaccination. Primed subjects have only been included in 2 studies: study MET56 included adolescent and adult subjects (15 to 55 years of age) previously vaccinated with a meningococcal quadrivalent conjugate vaccine and study MET51 included toddlers who received a monovalent MenC vaccination during infancy. No data for MenQuadfi vaccine are available from MenC-primed adolescents or adults.

Results are presented in the IB and MenQuadfi SmPC.

No data were available for MenQuadfi vaccine to boost itself.

Therefore, long-term persistence of immunogenicity beyond 30 days as well as the ability of MenQuadfi vaccine to boost itself were to be further investigated.

To assess the long-term immunogenicity of priming dose and safety and immunogenicity of booster in individuals primed with the MenACYW conjugate vaccine, the following studies have been conducted or are ongoing:

- Study MET62, an immunogenicity and safety study of a booster dose of MenACYW conjugate vaccine assessed antibody persistence in children 3 years after prior receipt of MenACYW conjugate vaccine as toddlers in study MET54.

  The results are presented in the IB and in this protocol.

- Study MET59, an immunogenicity and safety study of a booster dose of MenACYW conjugate vaccine that also assessed antibody persistence in adolescents and adults 3 to 6 years after prior receipt of MenACYW conjugate vaccine in study MET50. Individuals ≥ 13 to < 26 years of age at enrollment in MET59 study.

- Study MEQ00066, an immunogenicity and safety study of a booster dose of MenACYW conjugate vaccine that will also assess antibody persistence in older adults and elderly 3 to 7 years after prior receipt of MenACYW conjugate vaccine in studies MET44 and MET49. This study is ongoing in the US.

In Europe, a lifelong approach for meningococcal prevention with, in addition to the toddler and adolescent vaccination, a MenACYW preschool booster dose is recommended by some scientific societies as presented in the Calendario per la Vita developed conjointly by the Società Italiana di Pediatria, the Societa Italianadi Igiene, the Federazione Italiana Medici Pediatri, and the Federazione Italina Medici di Famiglia (29). It is already implemented in Italy, in the Tuscany region, with a booster dose given at 6-9 years of age (30).

In this context, generating boostability data approximately 5 and 10 years after a toddler dose, as well as immune persistence is of interest for Health Authorities.

The MEQ00073 study will evaluate the boostability of MenACYW conjugate vaccine in MenACYW conjugate vaccine-primed participants, and will provide longer persistence data than in the MET62 study, with a larger sample size (refer to Section 2.1).

MenACYW conjugate vaccine has been developed using titers measured by hSBA for the primary endpoints; titers measured by rSBA were also used as secondary endpoints in a subset of participants. Therefore, similar assays will be used in this study. The boostability will be determined by sufficiency for the primary objective of the study in children (who received 1 dose of MenACYW conjugate vaccine approximately 5 years earlier as toddlers) with the seroresponse measured using hSBA 30 days post booster dose administration in Group 1.

Since MenACYW conjugate vaccine has been evaluated in infants, toddlers, and adults without raising any safety concerns, safety assessment will be done up to 30 days after vaccination.

4.3 Justification for Dose

Participants in Group 1 will receive a first booster dose of MenACYW conjugate vaccine on D01 (V1) (at child age approximately 5 years post priming dose as toddlers in MET51) and a second

booster dose of MenACYW conjugate vaccine at Year 5 (V3) (at adolescent age approximately 5 years post booster dose as children in study MEQ00073). Participants in Group 2 will receive a single booster dose of MenACYW conjugate vaccine at Year 5 (V2) (approximately 10 years post priming dose as toddlers in study MET51) as per the current/intended indication in this age group for quadrivalent meningococcal conjugate vaccines.

4.4 End of Study Definition

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

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

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

5 Study Population

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

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

5.1 Inclusion Criteria

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

I01: Received MenACYW vaccine in MET51 study (Groups 1 and 3) and completed the study (attended V2)

I02: Assent form (AF) has been signed and dated by the participant (if applicable) and informed consent form (ICF) has been signed and dated by the parent(s) or another legally acceptable representative (LAR) and by an independent witness, if required by local regulations

I03: Participant and parent/LAR are able to attend all scheduled visits and to comply with all trial procedures

I04: 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:

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

E02: Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal

vaccine containing serogroups A, C, W, or Y) with the exception of licensed MenC vaccination received during infancy (MET51 Group 3), of the single dose of meningococcal vaccine administered as part of study MET51 (Groups 1 and 3) and of Meningococcal B vaccine

E03: Receipt of any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine in the 4 weeks following trial vaccination except for influenza vaccination, which may be received at least 2 weeks before or after study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines

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

E05: 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)

E06: History of meningococcal infection, confirmed either clinically, serologically, or microbiologically

E07: At high risk for meningococcal infection during the trial (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)

E08: Personal history of GBS

E09: Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine

E10: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[a]

E11: Verbal report by parent or LAR of thrombocytopenia or suspected thrombocytopenia, contraindicating IM vaccination

E12: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination

E13: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E14: Chronic illness[b] that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion

E15: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective participant

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

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases.

should not be included in the study until the condition has resolved or the febrile event has subsided

E16: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

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 may contact this physician (with the parent's/LAR's consent) to inform him/her of the participant's participation in the study. In addition, the site could 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

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

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

6 Study Intervention

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

Note: routine vaccines administered outside of study protocol are not considered as study interventions.

6.1 Study Intervention Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study intervention

Intervention Name	**MenACYW conjugate vaccine (MenQuadfi®)**: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Use	Investigational
IMP and NIMP	IMP
Type	Vaccine
Dose Formulation	Liquid solution
Unit Dose Strengths	Each dose of MenACYW conjugate vaccine contains the following components: Meningococcal capsular polysaccharides: • Serogroup A[1]: 10 µg • Serogroup C[1]: 10 µg • Serogroup W[1]: 10 µg • Serogroup Y[1]: 10 µg [1] Conjugated to Tetanus toxoid protein carrier: 55 µg[2] [2] Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation
Excipients/Diluent	Sodium acetate buffered saline solution
Dosage Level	0.5 mL per dose
Number of Doses/Dosing Interval	1 dose
Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm for children 3-17 years of age
Sourcing	Provided by the Sponsor

Packaging and Labeling	MenACYW conjugate vaccine (single-dose vial) will be supplied as an individual commercial box without repackaging. There will be no overlabel for primary packaging and a multilingual booklet label with clear tape on the outer box will be added. See the Operating Guidelines for additional label detail.
Current/Former Name or Alias	Brand name: MenQuadfi®
Batch Number	TBD

IMP: Investigational Medicinal Product; NIMP: Non-Investigational Medicinal Product; TBD: to be determined

6.2 Preparation/Handling/Storage/Accountability

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

It will be administered intramuscularly in the deltoid muscle of arm.

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.

Detailed guidance and information are provided in the Operating Guidelines.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

At V1, participants will be randomly selected with a balanced distribution between Groups 1 and 2 using SAS® software, Version 9.4 or above (SAS Institute, Cary, North Carolina, USA) to receive the same vaccine (MenACYW conjugate vaccine) at different timepoints.

Participant numbers will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). The 5-digit participant identified will correspond to the chronological order of enrollment in the center. For example, Subject 246000100005 is the fifth subject enrolled in Center Number 1 in Finland (246 being the country code for Finland).

Participant numbers should not be reassigned for any reason.

The Biostatistics platform of the Sponsor will generate a list of participants randomly selected (1 per site).

6.3.2 Blinding and Code-breaking Procedures

This is an open-label study.

6.4 Study Intervention Compliance

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

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

6.5 Concomitant Therapy

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

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

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

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

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

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

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

- Category 2: medications impacting or that may have an impact on the immune response and used to define the PPAS; for example:

  - Flu vaccines administered within 14 days pre or post each trial vaccination, including the day of the study vaccination visit and up to the last blood draw.
  - Any vaccine other than study vaccines (vaccines non-described in the Protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study vaccination visit and up to the last blood draw.
  - Immune globulins, blood or blood-derived products: used in the 3 months preceding each blood draw between BL1 to BL2 and BL3 to BL4 (Group 1) or between BL2 to BL3 (Group 2).
  - Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) used in the 3 months preceding the study vaccination, anti-cancer chemotherapy, anti-proliferative drugs such as deoxyribonucleic acid (DNA) synthesis inhibitors, or radiation therapy: used in the 6 months preceding the study vaccination between BL1 to BL2 and BL3 to BL4 (Group 1) and between BL2 to BL3 (Group 2).

  Category 2 medications will be reported in the CRB according to the collection period detailed above.

- Category 3: systemic (oral or injectable) antibiotics, received within 72 hours preceding each visit for blood draw related to IMP assessment (meningococcal vaccines) and used to define the PPAS, as they may interfere with bioassays used for antibody testing when taken before a blood draw.

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

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

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

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

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

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

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

6.5.1 Rescue Medicine

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

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

Not applicable.

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

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Contraindications for Vaccination

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.

TCI01: Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment

TCI02: Receipt of any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine in the 4 weeks following trial vaccination except for influenza vaccination, which may be received at least 2 weeks before or after study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines

TCI03: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the blood draw

TCI04: Receipt of immune globulins, blood or blood-derived products in the past 3 months

7.1.2 Temporary Contraindications for Blood Sample

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 would 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.

7.1.3 Definitive Contraindication

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 and immunogenicity. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

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

DCI01: Pregnancy, as indicated by a positive urine test

DCI02: An anaphylactic or other significant allergic reaction to the previous dose of vaccine

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

DCI04: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding vaccination.

DCI05: Receipt of immune globulins, blood or blood-derived products in the 3 months preceding vaccination

DCI06: Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y) with the exception of licensed MenC vaccination received during infancy (MET51 Group 3), of the single dose of meningococcal vaccine administered as part of study MET51 (Groups 1 and 3) and of Meningococcal B vaccine

DCI07: 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 3 months preceding vaccination)

DCI08: New history of meningococcal infection, confirmed either clinically, serologically, or microbiologically

DCI09: At high risk for meningococcal infection during the trial (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)

DCI10: New personal history of GBS

DCI11: New personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine

DCI12: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[a]

DCI13: Verbal report by parent or LAR of thrombocytopenia or suspected thrombocytopenia, contraindicating IM vaccination

DCI14: Chronic illness[b] that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion

In the event of a local or national immunization program with any other vaccine as needed, participants who receive such a vaccine at any time during the study will not be withdrawn from the study.

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

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases.

7.2 Participant Discontinuation/Withdrawal from the Study

- Parents/LARs will be informed that they have the right to withdraw their child from the study at any time.
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRB: Adverse Event, Lost to Follow-up, Protocol Deviation, or Withdrawal by Participant or Parent/LAR.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

Follow-up of Discontinuations

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

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

7.3 Lost to Follow-up

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

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

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

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

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable
- Exceptional situations (eg, COVID-19) may prevent access to the clinical trial sites. In these situations, site visits may be replaced by home visits where blood draw, physical examination and safety assessments will be performed by home nurses except for V1 (Group 1 and Group 2), V3 (Group 1), and V2 (Group 2), which will be conducted at the investigational site.

Blood samples will be collected as described in the SoA tables (Section 1.3). At V1 for all participants, 5 mL of blood will be collected in tubes provided by or recommended by the Sponsor. At V2, only participants in Group 1 who received study vaccination at V1 will provide a 5 mL blood sample. All participants are required to provide a blood sample at the Year 5 visit (V3 for Group 1, and V2 for Group 2) prior to receiving vaccination, and another blood sample 30 days post vaccination (V4 for Group 1 and V3 for Group 2).

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

8.1 Efficacy and Immunogenicity Assessments

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in a serum bactericidal assay utilizing the human complement (hSBA) and the baby rabbit complement (rSBA). The results will be expressed as vaccine seroresponse, seroprotection, and GMTs.

Antibodies to Meningococcal Antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in a serum bactericidal assay utilizing human complement. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with human complement are added to the serum dilutions and allowed to incubate. After this incubation period, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight at 37°C with 5% carbon dioxide (CO_2). Bacterial colonies present in the wells are then counted. The endpoint titer is determined by the reciprocal serum dilution yielding ≥ 50% killing as compared to the mean of the complement control wells. The lower limit of quantification (LLOQ) of the hSBA assay is a titer of 1:4.

The hSBA testing will be performed at [redacted]

Antibodies to Meningococcal Antigens (rSBA Method)

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

The rSBA testing will be performed at [redacted]

Antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine as a carrier protein will be determined in children who received MenACYW conjugate vaccine approximately 5 or 10 years earlier as toddlers. The results will be expressed as percentage of participants with antibody concentrations to tetanus toxoid ≥ 0.01 international units (IU)/mL and ≥ 0.1 IU/mL, and geometric mean concentrations (GMCs).

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

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

In this assay, each well of a 96-well microtiter plate is pre-coated in precise positions with the 6 different antigens in a multi-spot fashion. Following incubation with serum samples, antigen specific antibodies bind to the respective antigens. The captured antibodies are then detected using a sulfotag-conjugated anti-human immunoglobulin (Ig)G conjugate. Electrical stimulation of the conjugate in the presence of a chemiluminescent substrate results in the generation of a light signal from each specific spot that is captured by a camera in relative light units. The signal

generated is directly proportional to the amount of antibodies present in the sample, which is quantified using software and based on an established reference standard sample curve. For this study, only tetanus results will be calculated.

8.2 Safety Assessments

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

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

8.2.1 Medical History

Prior to enrollment at V1 (Groups 1 and 2) and before administration of the booster vaccination at V2 (Group 2) / V3 (Group 1), 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 CRB. The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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

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

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

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

8.2.2 Physical Examinations

A physical examination as per standard of care (physical examination, including, but not limited to, general examination of the main body systems of interest [heart, lungs, skin, neurologic, muscular-skeletal, lymphatic system, etc]) will be performed at V1 for both groups, and at V2 (Group 2) / V3 (Group 1) by the Investigator or a delegate.

Information will be recorded in the source document.

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

8.2.3 Vital Signs

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

8.3 Adverse Events and Serious Adverse Events

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

AEs will be reported by the participants/parents/LARs 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).

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

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

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

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

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

Unsolicited Non-serious Adverse Events

Unsolicited non-serious AEs will be collected from D01 to D31 after vaccination.

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

Adverse Events of Special Interest

AESIs will be collected throughout the study.

See Section 8.3.6 for the list of AESIs.

Serious Adverse Events

Information on SAEs will be collected and assessed throughout the study for both groups. However, for Group 2 before the first study intervention administration at V2, only SAEs related to study procedures (eg, blood sampling) are to be collected.

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

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 AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Individual DCs, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants' parents/LARs for the recording of daily safety information. These DCs will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants' parents/LARs will also be provided with rulers for measuring the size of injection site reactions, and with certified standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct participants' parents/LARs on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the participants' parents/LARs to collect the information recorded in the DC, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. Any information that was not documented in the DC will first be captured in the source document and then reported electronically.

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

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

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

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

- The AE is considered by the Investigator to be related to the study intervention administered.
- The AE caused the discontinuation of the participant from the study or from vaccination.

The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.
- For all studies except those investigating medical devices, 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.
- An Investigator who receives an Investigator safety report describing an 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.

8.3.5 Pregnancy

Pregnancy and/or the absence of the use of effective contraceptive methods, if required, will exclude vaccination at V3 (Group 1) / V2 (Group 2). However, a participant could potentially become pregnant during her participation.

Urine pregnancy testing will be performed, as applicable, before the V2 (Group 2) / V3 (Group 1) vaccination.

Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery, and recorded in the Pregnancy CRF. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.

- If a pregnancy is reported, the investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit it to the Sponsor within 1 month of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than [6 to 8 weeks] beyond the estimated delivery date, but will be in accordance with local regulations.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention until delivery or until delivery and end of lactation. However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

8.3.6 Adverse Events of Special Interest

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

- Generalized seizures (febrile and non-febrile) (31)
- Kawasaki disease (32) (33) (34)
- GBS (35)
- Idiopathic thrombocytopenic purpura (ITP) (36)

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. Further instructions on the data collection for these events and the relevant definitions will be provided in the CRB Completion Instructions.

8.4 Treatment of Overdose

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

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

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

8.5 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic 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 8.1.2) are evaluated in this study.

8.9 Immunogenicity Assessments

See Section 8.1.2.

8.10 Medical Resource Utilization and Health Economics

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

9 Statistical Considerations

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

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

9.1 Statistical Hypotheses

Primary objective

Thirty days after the administration of MenACYW conjugate vaccine at V1, the sufficiency of the percentages of participants in Group 1 who achieve an hSBA vaccine seroresponse for meningococcal serogroups A, C, W, and Y will be tested.

Details on statistical methods are provided in Section 9.4.

Secondary objectives

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

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

9.2 Sample Size Determination

All available and eligible participants, who participated in and completed the MET51 study (Groups 1 and 3) and received MenACYW conjugate vaccine as a part of the study, can be enrolled (approximately 500 participants), with approximately 250 participants each in MEQ00073 Group 1 and Group 2 (maximum estimate).

A sample size of 84 achieves at least 90.0% power to detect that the lower bound of the 1-sided 97.5% CI is greater than 0.75 (proportion under the null hypothesis) for the vaccine seroresponse to each serogroup using a 1-sided exact test with a significance level (alpha) of 0.025.

Table 9.1: Power of the study based on the primary objective

Antigen	Endpoint	Estimates* for MenACYW	Power (%)
A	Seroresponse	0.95	> 99.9
C	Seroresponse	0.90	92.6
Y	Seroresponse	0.95	> 99.9
W	Seroresponse	0.925	99.0
Global Power			> 90

*Estimated responses are based on the results of MET62 Group 1 that received 1 dose of MenACYW conjugate vaccine (estimates of MET62 minus 5%).

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Safety Analysis Set (SafAS)	• SafAS 1: Participants who have received the study vaccine 5 years after priming vaccination (at V1) and have any safety data available (Group 1). • SafAS 2: Participants who have received the study vaccine 10 years after priming vaccination at V3 (Group 1) / V2 (Group 2) and have any safety data available. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	The FAS will be duplicated for each FAS defined below: 1 each for hSBA and rSBA measurements. • FAS1: Subset of participants who received the study vaccine and had a valid post-vaccination serology result 5 years after priming vaccination at V1 (Group 1). Participants will be analyzed according to the intervention they received. • FAS2: Subset of participants who received the study vaccine and had a valid post-vaccination serology result 10 years after priming vaccination at V3 (Group 1) / V2 (Group 2). Participants will be analyzed according to the intervention they received. • FAS3: For persistence includes participants who have a valid serology result for at least 1 serogroup from a pre-vaccination blood sample (5-year antibody persistence, Group 1 and Group 2) • FAS4: For persistence includes participants who have a valid serology result for at least 1 serogroup from a pre-vaccination blood sample (10-year antibody persistence, Group 1 and Group 2)
PPAS	The PPAS will be duplicated for each PPAS defined below: 1 each for hSBA and rSBA measurements. The PPAS is a subset of the FAS. PPAS1 and PPAS2 will be defined: PPAS1 for Group 1 V1, and PPAS2 for Group 1 and Group 2 V3 and V2, respectively. Participants presenting with at

	least 1 of the following relevant protocol deviations will be excluded from the PPAS1 or PPAS2 as applicable. • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant did not receive vaccine • Participant received a vaccine other than MenACYW conjugate vaccine • 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 post-dose serology sample in the proper time window or a post-dose serology sample was not drawn • Participant received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine • Participant's serology sample did not produce a valid test result (ie, results for all meningococcal antigens are missing) • Participant had other protocol deviations that affected the participant's immune response, as determined by the clinical team before locking the database • Participant's serology sample did not produce a valid test result (ie, results for all meningococcal antigens are missing) • Participant had other protocol deviations that affected the participant's immune response, as determined by the clinical team before locking the database

9.4 Statistical Analyses

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

9.4.1 General Considerations

All immunogenicity analyses will be performed on the PPAS and on the FAS. All safety analyses will be performed on the SafAS.

9.4.2 Primary Endpoint

Thirty days after the administration of the MenACYW conjugate vaccine (approximately 5 years after priming as toddlers), the sufficiency of the percentages of participants in Group 1 who achieve an hSBA vaccine seroresponse (see definition below) for meningococcal serogroups A, C, W, and Y will be tested.

Seroresponse will be considered sufficient if lower limit of the 1-sided 97.5% CI calculated using the Exact method (Clopper-Pearson method) for percentage of participants with hSBA seroresponse against serogroups A, C, W and Y is greater than 75%.

This is equivalent to testing H0: $p \leq 0.75$ against H1: $p > 0.75$, where p is the observed proportion of subjects with hSBA seroresponse against serogroups A, C, W and Y. The CI for the single proportion will be calculated using the exact method (Clopper-Pearson method).

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

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

9.4.3 Secondary Endpoints

9.4.3.1 Immunogenicity

All analyses for the secondary endpoints will be descriptive; no hypotheses will be tested. Descriptive statistics will be provided for the hSBA and rSBA antibody titers against meningococcal serogroups (A, C, W, and Y) and for antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine as a carrier protein. The results will be expressed as vaccine seroresponse, seroprotection, and GMTs.

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

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

In summary, descriptive analyses of antibody responses to A, C, W, and Y serogroups for Group 1 (at V1 [baseline], V2 [30 days after the administration of a booster dose of MenACYW conjugate vaccine], and at V3 before the administration of a booster dose), V4 (30 days after the administration of a booster dose of MenACYW conjugate vaccine), and for Group 2 at V2 before the administration of a booster dose of MenACYW conjugate vaccine and at V3 (30 days after the administration of a booster dose of MenACYW conjugate vaccine) will include but not be limited to:

- hSBA and rSBA seroprotection rate (titer ≥ 1:8) and 95% CI

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

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

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

  rSBA vaccine seroresponse is defined as:

  - A post-vaccination rSBA titer ≥ 1:32 for participants with pre-vaccination rSBA titer < 1:8, or
  - A post-vaccination titer ≥ 4 times the pre-vaccination titer for participants with pre-vaccination rSBA titer ≥ 1:8

The hSBA and rSBA antibody titers against serogroup C will also be described for Group 1 at V1 (baseline) and V2 (30 days after the administration of a 5-year booster dose of MenACYW conjugate vaccine, and at V3 and V4 (30 days after administration of the second booster dose of MenACYW conjugate vaccine), and for Group 2 at V2 and V3 (30 days after administration of a 10-year booster dose of MenACYW conjugate vaccine) according to the priming status in infancy before receiving the toddler dose in MET51 study (meningococcal vaccine naïve or MenC-primed).

In addition, descriptive analyses on anti-tetanus antibody concentrations for Group 1 at V1 (baseline) and V2 (30 days after the administration of a 5-year booster dose of MenACYW conjugate vaccine, and at V3 and V4 (30 days after administration of the second booster dose of MenACYW conjugate vaccine, and for Group 2 at V2 and V3 (30 days after administration of a 10-year booster dose of MenACYW conjugate vaccine) will include but not be limited to:

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

Data from MET51 and MEQ00073 will also be combined and paired to evaluate antibody persistence and overall trends over 5 and 10 years.

9.4.3.2 Safety

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

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

9.4.4 Other Safety Analyses

Not applicable.

9.4.5 Other Analyses

Not applicable.

9.5 Interim Analyses

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study.

This study will include an interim analysis. A first statistical analysis of the immunogenicity and safety data collected up to V2 (Day 31) (Group 1) and V1 (Group 2), 5 years after priming dose in the MET51 study, will be performed once data are available and an interim database lock has been conducted. A final report will be prepared at the end of the entire study period.

9.6 Data Monitoring Committee (DMC)

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term "participant" is used throughout this protocol. However, the term "subject" will be used in the CRB in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR]).
- The protocol, protocol amendments, ICF, AF (if applicable), 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.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC [(in addition to summaries required from the Sponsor)].
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps
    - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and his/her parent/LAR and answer all questions regarding the study.
- Participants and their parents/LARs must be informed that their participation is voluntary. Participant's parents/LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- An AF will be signed and dated by the participant (if applicable) at enrollment (V1) and again after 5 years (V3 for Group 1 / V2 for Group 2) if required by local regulation. This form is to be used in addition to, not in place of, the ICF that is signed by the participant's parents/LARs.
- ICF may have to be signed and dated by an independent witness, if required by local regulations.
- 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 and AF (if applicable).
- The actual ICF and AF used at each center may differ, depending on local regulations and IEC/IRB requirements. However, all versions must contain the standard information found in the sample ICF and AF provided by the Sponsor. Any change to the content of the ICF and AF must be approved by the Sponsor and the IEC/IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's and participant's parents'/LARs' willingness to continue participation in the study, this will be communicated to him/her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF and via a revised AF or an addendum to the original AF (if applicable).
- Participants and their parents/LARs must be re-consented to the most current version of the ICF and AF during their participation in the study.
- A copy of the ICF and AF must be provided to the participants and their parents/LARs.

- The ICF will contain a specific section, if applicable, that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant and their parent/LAR the objectives of the exploratory research. Participants and their parents/LARs 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:

MEQ00073 is a study to be conducted in children approximately 6 to 7 years of age at enrollment (V1) and adolescents approximately 11 to 12 years of age at V2 (Group 2) or V3 (Group 1) to obtain immunogenicity and safety data in participants who were vaccinated with the MenACYW conjugate vaccine approximately 5 or 10 years earlier as toddlers (12 to 23 months of age) in the MET51 study (Group 1 and Group 3) and participants vaccinated with a booster dose of MenACYW conjugate vaccine approximately 5 years earlier as children in MEQ00073 study (Group 1).

Since these participants are unable to give their consent, written informed consent must be obtained from the parent or LAR 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/LAR in accordance with local practices. The parent/LAR should be able to consent for their child. The child of minor parents must not be included in the study.

The participants will be asked to date and sign an AF (if applicable).

Recruitment Procedures

Before the start of the trial, the Investigator or sub-investigator may contact the parents/LARs of an appropriate pool of potential participants (Group 1 and Group 3 of study MET51) and invite them to participate in the trial. The site will ensure that any advertisements used to recruit participants (eg, letters, pamphlets, posters) are submitted to Sanofi Pasteur before submission to the IEC/IRB for approval.

As this is a multi-center, multi-country study, the recruitment procedures will be described in a separate “Recruitment and consent process form” in each site. In such a case, the form will be archived on-site.

10.1.4 Data Protection and Future Use of Stored Samples

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

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

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participants' race and ethnicity will be collected in this study because these characteristics may influence the immune response to the vaccine.
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant's parent/LAR must be informed that the participant's personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant/parent/LAR as described in the informed consent.
- The participant's parent/LAR must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant's parent/LAR must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects.
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
    - Personnel within Sanofi or partners or service providers involved in the study
    - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the

framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency

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

10.1.5 Committees Structure

There will be no DMC. This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study.

10.1.6 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These

websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

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

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

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRB 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 CRB.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRB.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations [CROs]).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRB 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.
- Records and documents, including signed ICFs and AFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the

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

10.1.8 Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, DCs, medical and hospital records, screening logs, ICFs/AFs, telephone contact logs, and worksheets.

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

Detailed guidance and information are provided in the Operating Guidelines.

10.1.9 Study and Site Start and Closure

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

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

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The

Investigator shall promptly inform the participant/parent/LAR and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

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

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

10.2.1 Definition of Adverse Event

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

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

Events <u>NOT</u> Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

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

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

Immediate Event/Reaction:

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

Injection Site Reaction/Administration Site Reactions:

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

Systemic Adverse Event/Adverse Reaction:

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

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

Adverse Event of Special Interest:

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

Reactogenicity/Solicited Reactions

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

By definition, solicited reactions are considered as being related to the study intervention administered. For injectable vaccines, solicited reactions can either be solicited injection/administration site reactions or solicited systemic reactions.

Unsolicited Adverse Event/Adverse Reaction

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (headache starting on D10 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 CRB as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to study intervention. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

10.2.2 Definition of Serious Adverse Event

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

A Serious Adverse Event is defined as any untoward medical occurrence 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 detained (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 disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other important medical event

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

Note: *Serious* and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

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

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRB.
- 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 CRB pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

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

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the Investigator only.
  - For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the Global Pharmacovigilance (GPV) database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
- The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered[a] as either ***not related*** or ***related***, based on the following definitions:
  - Not related – The AE is clearly/most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable).
  - Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there is evidence or arguments to suggest a causal relationship.

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

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causal relationship in light of follow-up information and send a 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 Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRB.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- AEs likely to be related to the study intervention, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.2.4 Reporting of Serious Adverse Events

Serious Adverse Event Reporting to the Sponsor via an Electronic Data Collection Tool

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

Serious Adverse Event Reporting to the Sponsor via Paper Case Report Book

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

    Reception and Triage – Case Management
    Global Pharmacovigilance
    Mail Drop: 45D38
    Discovery Drive
    Swiftwater, PA 18370

Safety Emergency Call

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

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

10.2.5 Assessment of Intensity

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

10.2.5.1 Tables for Clinical Abnormalities

10.2.5.1.1 Solicited Adverse Reaction Intensity Grading Scale

Table 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales – Children at V2 (Group 1)

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
DC term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	**CRB:** Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities **DC:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

Abbreviations: DC, diary card; MedDRA, Medical Dictionary for Regulatory Activities
* For the subjective reaction of pain, participants or parents/LARs will record the intensity level (Grade 1, 2, or 3) in the DC. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.
Note: This table is to be used for Group 1 at V2.

Table 10.2: Solicited injection site reactions: terminology, definitions, and intensity scales – Adolescents and adults aged ≥ 10 years at V4 (Group 1) and V3 (Group 2)

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

MedDRA: Medical Dictionary for Regulatory Activities
* For pain, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.
Note: This table is to be used for Group 1 at V4 and for Group 2 at V3.

Important notes for the accurate assessment of temperature:

Participants or parents/LARs are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is axillary (rectal or oral may be also used). A certified standard digital thermometer should be used. Other types of thermometer (tympanic scan, temporal artery scan and infrared skin scan) are not allowed.

10.2.5.1.2 Unsolicited Adverse Event 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 Appendix 10.2.5.1.1).

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

- Grade 1
  - CRB: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - DC: No interference with activity.
- Grade 2
  - CRB: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - DC: Some interference with activity.
- Grade 3
  - CRB: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - DC: Significant; prevents daily activity.

10.3 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.

10.4 Appendix: Abbreviations

AE	adverse event
AESI	adverse event of special interest
AF	assent form
AR	adverse reaction
BL	blood sample
CDISC	Clinical Data Interchange Standards Consortium
CFU	colony-forming unit
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CO_2	carbon dioxide
CRB	case report book
CRO	Contract Research Organization
D	Day
DC	diary card
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTP-ECL	diphtheria, tetanus, pertussis multiplexed electrochemiluminescent
ECG	electrocardiogram
ECDC	European Center for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
[redacted]	[redacted]
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMC	geometric mean concentration
GMT	geometric mean titer
GMTR	geometric mean titer ratio

GPV	Global Pharmacovigilance
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papillomavirus
hSBA	serum bactericidal assay using human complement
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IU	international unit
LAR	legally acceptable representative
LLOQ	lower limit of quantification
LLT	lowest level term
MCV4-CRM	meningococcal conjugate vaccine quadrivalent
MedDRA	Medical Dictionary for Regulatory Activities
MenC	meningococcal C
NIMP	non-investigational medicinal product
NSAID	non-steroidal anti-inflammatory drug
PPAS	Per-protocol Analysis Set
PS	polysaccharide
RCDC	Reverse cumulative distribution curve
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay 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
TC	telephone call
Tdap	tetanus, diphtheria, and acellular pertussis
TESSy	The European Surveillance System

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12 Sponsor Signature Page

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VV-TMF-1720568 MEQ00073 protocol v1.0

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