NCT04936685

SAP Core Body

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

Study Phase: Phase IIIb

SAP Core Body Version: 1.0

SAP Core Body Date: 26 July 2023

Protocol Version Number: 2.0

The SAP Code Body should be used in conjunction of the study protocol and the SAP TLF (if applicable).

Version History

Not applicable as this is the first version of the SAP Core Body.

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Overall Design

The design of the study is summarized in Table 1.1.

Table 1.1: Overall design

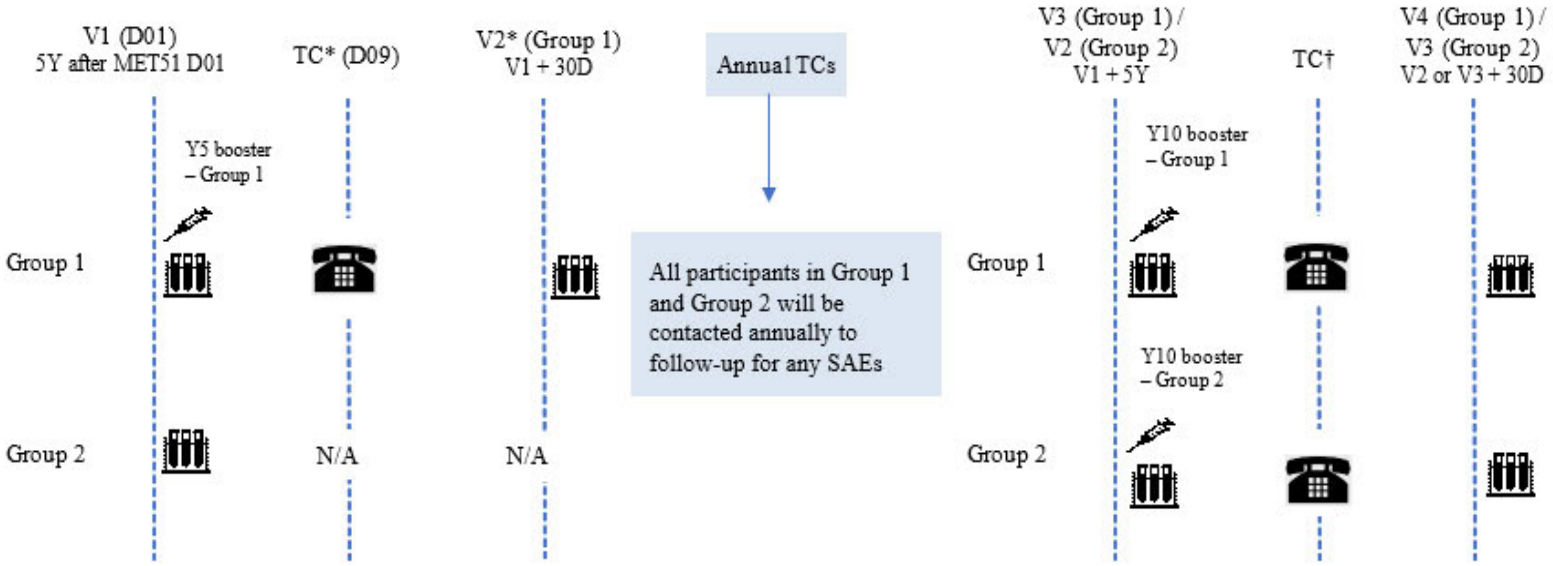
Type of design	open-label, multi-center and multi-country
Phase	IIIb
Control method	uncontrolled
Study population	Healthy children approximately 6 to 7 years of age at the time of enrollment who were vaccinated with MenACYW conjugate vaccine approximately 5 years earlier as toddlers (12 to 23 months 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 (first booster dose) at D01 (V1) and a dose of MenACYW conjugate vaccine (second booster dose) at Year 5 (V3). Participants in Group 2 will receive a single booster 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

The study design is presented in Figure 1.1

The schedule of activities for Group 1 are given in Table 1.2 and for Group 2 are given in Table 1.3.

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)

Table 1.2: 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		
Urine pregnancy test (if applicable)									X		
Review warnings and precautions and / or contraindications for vaccination	*X*	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
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		
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

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
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 1.3: 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		
Review of temporary contraindications for blood sampling†	*X*	X					X		X
Blood sample (BL), 5 mL		BL1					BL2‡		BL3

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
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
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. Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 2.1

Table 2.1: Objectives and endpoints.

Objectives	Endpoints
Primary	
• To demonstrate the vaccine seroresponse sufficiency (cf 1.4.2) 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

3. Statistical Considerations

1.1. 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.

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).

1.2. 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 3.1: 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%).

1.3. Populations for Analyses

The following populations are defined:

Population	Description
Study participants with data in CRF**Error! No document variable supplied.**	All study participants included in the table shells are study participants with a Case Report Form (CRF) (i.e., with data in the clinical database).
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. SafAS: Participants who have received at least one dose of the study vaccine. All participants will have their safety analyzed after any dose according to the vaccine received at the 1st dose. All participants will have their safety analyzed according to the vaccine scheme 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 (hSBA or rSBA accordingly) 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 (hSBA or rSBA accordingly)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 had a valid baseline serology result (hSBA or rSBA accordingly) (5-year antibody persistence, Group 1 and Group 2) FAS4: For persistence includes participants who had a valid pre-vaccination serology result (hSBA or rSBA accordingly) (5-

	year antibody persistence after the first booster dose in Group 1, 10-year antibody persistence in Group 2). Participants will be analyzed according to the intervention they received.
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 at 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

Safety analyses after MenACYW conjugate vaccine received at V01 in Group 1 will be performed on SafAS 1. Safety analyses after MenACYW conjugate vaccine received at V03 in Group 1 and at V02 in Group 2 will be performed on SafAS2.

Immunogenicity analyses will be performed on:

- PPAS1 for the description of immune response to the MenACYW conjugate vaccination received at V01 in Group 1, and on FAS1 if the attrition rate from FAS1 to PPAS1 is greater than 10%.

- FAS3 for the persistence assessment in participants receiving approximately 5 years earlier as toddlers (Groups 1 and 2)
- PPAS2 for the description of immune response to the MenACYW conjugate vaccination received at V03 in Group 1 and at V02 in Group 2, , and on FAS2 if the attrition rate from FAS2 to PPAS2 is greater than 10%.
- FAS4 for the 5-year antibody persistence after the first booster dose in Group 1, and for the 10-year antibody persistence in Group 2. Group 1 and Group 2 will be described separately.

When applicable, the above populations will be duplicated for hSBA and rSBA measurements.

1.4. Statistical Analyses

1.4.1. General Considerations

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

For descriptive purposes, the following statistics will be presented:

Table 3.2: Descriptive statistics produced

Disposition and follow-up description	**Categorical data**	At least number of subjects (Percentage of subjects are also possible).
	Continuous data	Mean, standard deviation, [quartiles,] minimum and maximum.
Baseline characteristics	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs for main endpoints) of subjects. Unsolicited: Number and percentage (95% CIs for main endpoints) of subjects and number of events.
Immunogenicity results	**Categorical data (seroprotection, cutoff)**	Number and percentage (95% CIs for main endpoints) of subjects.
	Continuous data (titer / data)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum.

		Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1), i.e., using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

1.4.2. 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

1.4.3. Secondary Endpoints

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,GMTs, and titers greater or equal to a specific threshold.

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 for serogroups A, C, W, and Y 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 (data at baseline will be pooled for Group 1 and Group 2 for 5-years persistence after priming in MET51) to evaluate antibody persistence and overall trends over 5 and 10 years. Kinetic curves will also be presented to describe persistence.

In addition, immunogenicity will be described according to sex, as appropriate according to number of participants in the respective subgroups.
Subgroup analyses will be performed on PPAS.

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.

In addition, the main safety endpoints will be described according to sex , as appropriate according to number of participants in the respective subgroups.

1.4.4. Handling of Missing Data and Outliers

Generally, no replacement will be done for Safety Missing Data and Outliers.

1.4.4.1. Safety

1.4.4.1.1. Immediate

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

1.4.4.1.2. Causal Relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

1.4.4.1.3. Intensity

For solicited reactions, missing intensities will be handled as described in Section 1.8.1.1.1.For unsolicited AEs, missing intensities will remain missing and will not be imputed.

1.4.4.1.4. Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the last vaccination (computed according to the Section 1.8.1.2.3). If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

1.4.4.1.5. Action Taken

Missing actions taken will remain missing and not be imputed.

1.4.4.2. Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described in Section 4.2.3.1.

1.5. Interim Analysis

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.

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. The interim study report (5-year report) will include immunogenicity data from hSBA and safety data collected up to V2 (Day 31) (Group 1) and V1 (Group 2), 5 years after priming dose in the MET51 study .

The study reports at 5 years and 10 years after priming dose may not include the rSBA immunogenicity data in case of delays with the rSBA testing. The rSBA data will be presented in that case in a CSR addendum at the time of availability. .

A final analysis (10-year report after priming dose) will be performed at the end of the study period.

1.6. Data Monitoring Committee (DMC)

Not applicable.

4. Complementary Information on Assessment Methods

Study assessments and procedures are detailed in Section 8 of the protocol. This section focusses on complementary/additional information not detailed in the protocol.

1.7. Complementary Information for Endpoint[s] Assessment Method[s]

1.8. Complementary Information on Derived Endpoints: Calculation Methods

1.8.1. Safety

1.8.1.1. Solicited Reactions

1.8.1.1.1. Daily Intensity

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

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

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as “No” and with all daily records missing (Unknown) then all daily intensities will be derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non measurable, “NM”) is Grade 3. Note the intensity could be considered “None” (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

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

Table 4.1 :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 4.2 :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.

Table 4.3 : Solicited systemic reactions: terminology, definitions, and intensity scales – Children 2 through 11 years of age, adolescents or adults ≥ 12 years of age

CRB term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**
DC term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**CRB:** Grade 1: 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.	**CRB:** Grade 1: 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.	**CRB:** Grade 1: 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.

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: 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.	Grade 2: 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.	Grade 2: 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.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
		DC:	**DC:**	**DC:**
		Grade 1: No interference with usual activities	Grade 1: No interference with usual activities	Grade 1: No interference with usual activities
		Grade 2: Some interference with usual activities	Grade 2: Some interference with usual activities	Grade 2: Some interference with usual activities
		Grade 3: Significant; prevents usual activities	Grade 3: Significant; prevents usual activities	Grade 3: Significant; prevents usual activities

Abbreviations: DC, diary card; MedDRA, Medical Dictionary for Regulatory Activities

* For all reactions but fever, participants or parents/LARs will record the intensity level (Grade 1, 2, or 3) in the DC. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

1.8.1.1.2. Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 1.8.1.1.1 is calculated as the maximum of the daily intensities over the period considered.

1.8.1.1.3. Presence

Presence is derived from the maximum overall intensity over the time period considered:

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

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

The time period is displayed as D1-D4, D5-D8, D9 and later.

1.8.1.1.4. Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 1.8.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

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

Time of onset period is displayed as, D1-D4, D5-D8.

1.8.1.1.5. Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 1.8.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

1.8.1.1.6. Overall Number of Days of Occurrence

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

(End date - last vaccination date) + (number of days of presence within the solicited period) - length of the solicited period + 1

If the end date is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

1.8.1.1.7. Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 1.8.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

1.8.1.2. Unsolicited AEs

1.8.1.2.1. Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

Grade 0 events are not included in safety analysis but are included in separate listings.

1.8.1.2.2. Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but < 25 mm in adults).

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

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

1.8.1.2.3. Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the CRF and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE
- If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE.

1.8.1.2.4. Time of Onset

Time of Onset = start date of the unsolicited AE - date of last vaccination before the unsolicited AE + 1 (if D1 is the first vaccination day).

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

The unsolicited AEs will be analyzed "Within 30 days" after each vaccination, which corresponds to AEs with a time of onset <between 1 and 31 days> or missing / between injection and the next visit or missing (upper limit of the time window of the next visit if visit not done)>. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the section 3.1.4.2.3), so will be included in these tables.

Time of onset period is displayed as D1-D4, D5-D8, D9-D15, D16 or later, and Missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) <or with a time of onset higher than defined above> will not be included in analysis but will be listed separately.

1.8.1.2.5. Duration

Duration is derived from the start and end dates of the unsolicited AE:

Duration = End date of unsolicited AE - start date of unsolicited AE + 1.

The duration is considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

1.8.1.2.6. Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

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

- Within 7 days after vaccination
- Within 30 days after vaccination
- During the study (i.e., all SAEs occurred during the study)

1.8.1.2.7. Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF.

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

- Within 7 days after vaccination
- Within 30 days after vaccination
- During the study (i.e., all AESIs occurred during the study)

1.8.2. Other Safety Endpoints

1.8.2.1. Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

1.8.2.2. Action Taken

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

1.8.2.3. Seriousness

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

1.8.2.4. Outcome

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

1.8.2.5. Causal Relationship

This information will be summarized as collected in the field "Relationship to study vaccine". Missing causal relationship will be handled as described in Section 1.4.4.1.2. Relationship to study procedure is only presented in the listing.

1.8.2.6. Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Study" form question "What was the participant's status?" has "Adverse Event" checked.
- Safety overview table: A participant who has either on the "Completion at End of Study" form, question" What was the participant's status?" has "Adverse Event" checked or lists a

solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

- System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

1.8.3. Immunogenicity

1.8.3.1. Computed Values for Analysis

In order to appropriately manage extreme values (undetectable responses < the lower limit of quantitation [LLOQ] and ≥ the upper limit of quantitation [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

1.8.3.2. Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows:

- Calculate the fold-rise of values as the ratio of post-baseline computed value divided by baseline computed value

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

1.8.3.3. hSBA Vaccine Seroresponse

The derived vaccine seroresponse indicator for hSBA will be "Yes" if:

- hSBA titer is < 1:8 at baseline with a post-baseline hSBA titer ≥ 1:16
- or hSBA titer is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-baseline

1.8.3.4. rSBA Vaccine Seroresponse

The derived vaccine seroresponse indicator for rSBA will be "Yes" if:

- rSBA titer is < 1:8 at baseline with a post-baseline rSBA titer ≥ 1:32
- or rSBA titer is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-baseline

1.8.4. Efficacy

Not applicable.

1.8.5. Derived Other Variables

1.8.5.1. Age for Demographics

The age of a subject in the study was the calendar age in years at the time of inclusion.

1.8.5.2. Duration of a Subject in the Trial

The duration of a subject in the study is computed as follows:

Maximum (date of last visit, date of termination) – (date of Visit 1 of that subject) +1.

1.8.5.3. Duration of the Study

The duration of the study is computed as follows:

Maximum of all subjects (date of last visit, date of termination) – Minimum of all subjects (date of Visit 1) + 1.

1.8.5.4. Time Interval

The time interval between 2 study timepoints (visits/vaccination/blood samples) is computed as follows:

Later date – earlier date.

1.8.5.5. MenC primed status

Participants who have received monovalent MenC vaccination during infancy are considered as “Primed” whereas participants who haven’t received monovalent MenC vaccination during infancy is considered as “Naïve”. The MenC primed status is defined according to the priming status in infancy before receiving the toddler dose in MET51 study

5. Changes in the Conduct of the Trial or Planned Analyses

Not applicable.

6. Supporting Documentation

1.9. Appendix 1 List of Abbreviations

AE	adverse events
AESI	adverse events of special interest
AR	adverse reaction
CI	confidence interval
D	day
DC	diary card
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECDC	European Center for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
FSH	follicle stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
GM	Geometric mean
GMT	Geometric mean of titer
GMC	Geometric mean of concentration
GPV	Global Pharmacovigilance
hSBA	serum bactericidal assay using human complement
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology

IU	international units
LLOQ	lower limit of quantification
LLT	lowest level term
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MenC	meningococcal serogroup C conjugate vaccine
NA	Not applicable
NC	Not computed
NIMP	non-investigational medicinal product
PPAS	Per-Protocol Analysis Sets
PRN	pertactin
PT	pertussis toxoid
PT	Preferred term
RCDC	Reverse cumulative distribution curve
rSBA	serum bactericidal assay using baby rabbit complement
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SmPC	summary of product characteristics
SOC	(Primary) System organ class
TC	telephone call
TLF	Tables, listings and figures
VLP	virus-like particle
ULOQ	Upper level of quantitation
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

7. References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in medicine. 1998;17(8):857-72.

2. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998;17(8):873-90.