NCT Number: NCT03476135

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered as a Booster Dose in Children Vaccinated 3 Years Earlier as Toddlers

A Phase III, open-label, multi-center study 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 in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix® as part of the MET54 study.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET62
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Products:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular (IM)
Indication For This Study:	Meningococcal conjugate vaccine as a booster dose in children vaccinated 3 years earlier as toddlers
Version and Date of the SAP core body part:	Version 1.0, 30SEP2018

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CI	confidence interval
CRF	(electronic) case report form
CSR	clinical study report
D	day
DC	diary card
dil	dilution
FAS	full analysis set
FASP	full analysis set for persistence
FDA	Food and Drug Administration
GM	geometric mean
GMC	geometric mean concentration
GMT	geometric mean titer
IU	international unit
LLOQ	lower limit of quantification
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
PPAS	per-protocol analysis set
PT	preferred term
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SOC	system organ class (primary)
TLF	table(s), listing(s), and figure(s)
ULOQ	upper limit of quantification
V	visit

1 Introduction

This study (MET62) will assess the immunogenicity and safety of a booster dose of the investigational quadrivalent Meningococcal Polysaccharide (serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) administered 3 years after a primary dose of MenACYW conjugate vaccine or Nimenrix® was administered to toddlers participating in the MET54 study. The persistence of the immune response against meningococcal serogroups A, C, Y, and W, 3 years after primary vaccination with either MenACYW conjugate vaccine or Nimenrix®, will also be described.

The epidemiology of Neisseria meningitidis (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 incidence rate of Invasive meningococcal disease (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 year old group. The highest incidence rate in Europe is caused by serogroup B, followed by C (1). 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 aged 65 years and above. Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in 2013 - 2014 compared with an average of 1% to 2% of all IMD cases in earlier years (2). A gradual increase in serogroup Y IMD has also been recently reported in Sweden during 2005 – 2012 (3) (4). Nearly 50% of all IMD was caused by serogroup Y in 2012 (3). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Scandinavian countries, accounting for 31% in Norway in 2009 – 2010 and 38% in Finland in 2010 (5).

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 including children as young as 6 weeks of age, adolescents, and adults, including those 56 years of age and older. MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. Based on the data generated from previous studies, the immunogenicity profile of the MenACYW conjugate vaccine in different age groups shows that the majority of subjects developed seroprotective levels of antibodies after vaccination. Compared to the currently-licensed in many regions Sanofi Pasteur meningococcal conjugate vaccine, Menactra®, the MenACYW conjugate vaccine is prepared using tetanus toxoid as the carrier protein. Conjugation of polysaccharide antigens to a protein carrier can induce T-cell-dependent immune responses, which are anticipated to give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response.

The purpose of MET62 is 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 in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix® as part of the MET54 study.

2 Trial Objectives

Immunogenicity

1) To describe the antibody persistence of meningococcal serogroups A, C, Y, and W before a booster dose in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

2) To describe the antibody responses to meningococcal serogroups A, C, Y, and W 30 days after a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

3) To describe the antibody responses against tetanus toxoid 30 days after a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

Safety

To describe the safety profile of a booster dose of MenACYW conjugate vaccine in children who received either MenACYW conjugate vaccine or Nimenrix® 3 years earlier as toddlers

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase III, open-label, multi-center study 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 in Finland who had been vaccinated 3 years earlier as toddlers with either MenACYW conjugate vaccine or Nimenrix® as part of the MET54 study.

Subjects who were vaccinated 3 years (± 45 days) earlier at 12 to 23 months of age in study MET54 were eligible for enrollment in study MET62.

All subjects were to receive a single dose of MenACYW conjugate vaccine on Day (D) 0.

All subjects were to provide blood samples (BL) for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days after vaccination.

Solicited adverse event (AE) information was to be collected for 7 days after vaccination; unsolicited AE information was to be collected from Visit 1 (D0) to Visit 2 (D30 [+14 days]), and serious adverse event (SAE) information (including adverse events of special interest [AESIs]) was to be collected throughout the study period.

3.2 Trial Plan

A schedule of assessments and study vaccinations is provided in the Table of Study Procedures.

Vaccination

All subjects were to receive a single dose of MenACYW conjugate vaccine at Visit 1 (D0).

Blood Sampling

All subjects were to provide a pre-vaccination blood sample on D0 and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination at Visit 1).

Collection of Safety Data

- All subjects were to be observed for 30 minutes after vaccination and any unsolicited systemic AEs occurring during that time were to be recorded as immediate unsolicited systemic AEs in the electronic case report form (CRF).
- The subject's parent / legally acceptable representative was to record information in a diary card (booklet or electronic device [e-diary]) about solicited reactions from D0 to D07 after vaccination and unsolicited AEs from D0 to Visit 2. SAEs were to be reported throughout the duration of the trial.
- In addition, the subject's parent / legally acceptable representative were to be asked to notify the site immediately about potential SAEs at any time during the trial.
- Alerts were to be sent to the e-diary (if applicable) and staff were to contact the subject's parent / legally acceptable representative by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported, and to remind them to complete the diary card (booklet or e-diary) up to Visit 2 and to bring it back at Visit 2.
- The completed diary card (booklet or e-diary) was to be reviewed with the subject's parent / legally acceptable representative at Visit 2.

Note: The diary card may be either a booklet or an electronic device that contains an application to enter the information (e-diary).

Table 3.1: Study procedures

Phase III Study, 2 Visits, 1 Vaccination, 2 Blood Samples, 1 Telephone Call, 30 Days Duration per Subject

Visit/Contact	**Visit 1**	**Telephone Call 1**	**Visit 2**
Trial timelines (days)	D0	D08	D30
Time windows (days)	--	+2 days	+14 days
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Medical history	X		
Physical examination*	X		
Review of temporary contraindications for blood sampling†			X
Allocation of subject number	X		
Blood sampling (BL), 5 mL‡	BL1		BL2
Vaccination§	X		
Immediate surveillance (30 minutes)	X		
Diary card (booklet or e-diary) provided	X		
Telephone call		X**	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited AEs	D0 to Visit 2		
Reporting of SAEs (including AESIs)††	To be reported throughout the study period		
Diary card (booklet or e-diary) reviewed and collected			X
Collection of reportable concomitant medications	X		X
Trial termination record			X

*Temperature needs to be measured and recorded in source documents.

† Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of the 30 to 44 day timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

‡ Blood sample at Visit 1 will be drawn before administration of vaccine

§ Subjects will receive 1 dose of MenACYW conjugate vaccine

** This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE, including AESIs, not yet reported, and will remind the subject's parent / legally acceptable representative to continue using the diary card (booklet or e-diary) up to Visit 2, to bring the diary card (booklet or e-diary) to the study center at Visit 2, and confirm the date and time of Visit 2. Additionally, an alert may be sent to the e-diary (as applicable) to remind the subject's parent / legally acceptable representative to report any SAEs, including AESIs, not yet reported and to continue to use the e-diary up to Visit 2, to bring the e-diary to the study center at Visit 2, and confirm the date and time of Visit 2.

†† 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.

4 Endpoints and Assessment Methods

4.1 Immunogenicity

See Section 9.1 of the protocol.

4.2 Safety

See Section 9.2 of the protocol.

4.3 Efficacy

No clinical efficacy data will be obtained in the study.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 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.

For measurable injection site reactions (Erythema/Swelling):

Grade 1: > 0 to < 25 mm

Grade 2: ≥ 25 to < 50 mm

Grade 3: ≥ 50 mm

For measurable systemic reactions (Fever):

Grade 1: ≥ 38.0°C to ≤ 38.4°C

Grade 2: ≥ 38.5°C to ≤ 38.9°C

Grade 3: ≥ 39.0°C

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

1) Solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as “No” and with all daily records missing then all daily intensities will be derived as None.
2) For a temperature partially missing after decimal point, the data will be analyzed replacing “MD” (missing data) by zero. For example, a “39.MD” daily temperature will be considered as "39.0°C" at the time of analysis.

3) For non-measurable solicited reactions, the daily intensities will correspond to the 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 that a reaction that is too large to measure (non measurable, "NM") is Grade 3. 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.

4.4.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

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

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. 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.

Categories for time of onset are as follows

- D0-D3
- D4-D7

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

Categories for number of days of occurrence during the solicited period are as follows

- 1-3 days

- 4-7 days
- 8 days

4.4.1.1.6 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 occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

- (stop date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the stop date is missing or incomplete (contains missing data [MD]), the overall number of days of occurrence will be considered as Missing.

Categories for overall number of days of occurrence are as follows

- 1-3 days
- 4-7 days
- ≥ 8 days
- Missing

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 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. Note: The intensity could be considered None (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., fever > 37.5°C but < 38°C). If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

4.4.1.2 Unsolicited Non-serious AEs

4.4.1.2.1 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 should be included in the listing "Unsolicited non-serious adverse events not included in the safety analysis."

4.4.1.2.2 Intensity

Intensity for unsolicited non-serious AEs will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited non-serious AE is measurable and its preferred term (PT) is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule as the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the CRF.

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

4.4.1.2.3 Last Vaccination

Last vaccination before an unsolicited non-serious AE is derived from the visit numbers provided in the clinical database and is calculated as follows:

- If an unsolicited non-serious AE has a non-missing visit number, the visit number should be used to determine the last vaccination before the unsolicited non-serious AE
- If the visit number is missing, then the start date should be used to determine the last vaccination before the unsolicited non-serious AE

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

- start date of the unsolicited non-serious AE – date of previous vaccination

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

The unsolicited non-serious AEs will be analyzed “Within 30 days”, which corresponds to AEs with a time of onset between D0 and D30 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: Unsolicited non-serious 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.

Time of onset will be displayed as follows:

- D0-D3
- D4-D7
- D8-D14
- ≥ D15
- Missing

4.4.1.2.5 Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

- stop date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if one or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

Duration will be displayed by period as following:

- 1-3 days
- 4-7 days
- 8-14 days
- ≥ 15 days
- Missing

4.4.1.3 SAEs

4.4.1.3.1 Last Vaccination

Last vaccination before an SAE is derived from the visit numbers provided in the clinical database and is calculated as follows:

- If an SAE has a non-missing visit number, the visit number should be used to determine the last vaccination before the SAE
- If the visit number is missing, then the start date should be used to determine the last vaccination before the SAE

4.4.1.3.2 Time of Onset

Time of onset will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.4.

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

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

An SAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: SAEs that occurred before vaccination (negative time of onset) will not be included in analysis, but will be listed separately.

4.4.1.3.3 Duration

Duration will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.5.

4.4.1.4 Other Safety Endpoints

4.4.1.4.1 Pregnancy

Not applicable for this study.

4.4.1.4.2 Action Taken

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

4.4.1.4.3 Seriousness

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

4.4.1.4.4 Outcome

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

4.4.1.4.5 Causality

This information will be summarized as collected. An adverse reaction (AR) is defined as an unsolicited non-serious AE or an SAE with causality to the vaccine. Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.4.6 AEs Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination "Serious Adverse Event" or "Other adverse event" is checked
- Safety overview table: A subject who has either on the termination form, the reason for early termination "Serious Adverse Event" or "Other adverse event" is checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked that is at least Grade 1 and is within the time period indicated
- SOC/PT table: An event (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked that is at least Grade 1 and is within the time period indicated

4.4.1.4.7 AEs of Special Interest

[redacted]

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

In order to appropriately manage extreme values (< LLOQ and ≥ ULOQ) for analysis purposes, the following computational rule will be applied to the values provided in the clinical database for each BL drawn:

In order to appropriately manage replicate values for analysis purposes, the individual GM of all values will be computed for each BL after managing extreme values as described:

- 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

4.4.2.2 Seroprotection

Not applicable

4.4.2.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and will be computed using the FDA definition as follows. Generally, for extreme values, this algorithm minimizes the numerator and maximizes the denominator.

- If the baseline computed value is < LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is 1
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value / baseline computed value
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is (LLOQ/2)/baseline computed value
- If the baseline computed value is < LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value / LLOQ

If the computed value is ≥ 4-fold rise, then the derived ≥ 4-fold rise indicator will be “Yes” for that test, otherwise ≥ 4-fold rise will be "No".

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

4.4.2.4 Seroconversion

Not applicable

4.4.2.5 Seroresponse

hSBA vaccine seroresponse (definition proposed by the Center for Biologics Evaluation and Research [CBER] in 2016) for serogroups A, C, Y, and W 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.

hSBA vaccine seroresponse (definition used in study MET54) for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:8.
- 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.

rSBA vaccine seroresponse is defined as:

- a post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8,

  or
- a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8.

4.4.3 Efficacy

Not applicable

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

The age of a subject in the study is the calendar age as defined in the protocol.

4.4.4.2 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.

4.4.4.3 Duration of the Study

The duration of the study is computed in days as follows:

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

5 Statistical Methods and Determination of Sample Size

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

The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**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) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (seroresponse, ≥4-fold rise, cutoff)**	Number and percentage (95% CIs) 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 CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (6), 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.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Trial Objectives

No hypotheses will be tested.

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

5.1.1.1 Hypotheses

No hypotheses will be tested.

5.1.1.2 Statistical Methods

5.1.1.2.1 Immunogenicity

Descriptive statistics will be provided for the hSBA and rSBA antibody titers against meningococcal serogroups (A, C, Y, and W) and for antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine.

In general, categorical variables will be summarized and presented by frequency counts, proportion percentages, and confidence intervals (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 (6). For geometric mean titers (GMTs), 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

RCDC figures will be provided for the antibody titers against meningococcal serogroups or antibody concentrations against tetanus toxoid contained in MenACYW conjugate vaccine.

In summary, descriptive analyses on A, C, Y, and W serogroups on D0 and D30 (+14 days) will include but not be limited to:

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

In summary, descriptive analyses on anti-tetanus antibody concentrations on D0 and D30 (+14 days) will include but not be limited to:

- Geometric mean concentrations (GMCs) and 95% CI

- The percentage of subjects with antibody concentrations to tetanus toxoid ≥ 0.01 international units (IU)/mL, ≥ 0.1 IU/mL, and ≥1 IU/mL, and 95% CI

Data from MET54 and MET62 will also be combined and paired to evaluate antibody persistence and overall trend over 3 years. The data to be compared from these two studies will include but not be limited to the following endpoints on D0 (baseline) and D30 in toddlers after having received a single dose of either MenACYW conjugate vaccine or Nimenrix®, as part of study MET54, and on D0 (baseline) and D30 in children after receiving a booster dose of MenACYW, as part of study MET62.

- hSBA and rSBA GMTs and 95% CI
- Percentage of subjects with hSBA titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of subjects with rSBA titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Geometric mean of anti-tetanus antibody concentrations and 95% CI
- The percentage of subjects with antibody concentrations to tetanus toxoid ≥ 0.01IU/mL and ≥ 0.1 IU/mL

Kinetics curves for hSBA and rSBA GMTs, and tetanus GMC including the 4 time points will also be provided.

5.1.1.2.2 Safety

For this trial, the safety data will be assessed by applying descriptive statistical methods, supplemented by the calculation of CIs to aid interpretation. The exact binomial distribution (Clopper-Pearson method) for proportions will be used in the calculation of the 95% CIs of events.

The frequency and percentage of subjects who had solicited injection site and systemic reactions and their 95% CIs will be provided. These events will be tabulated by type of reactions and intensity for each study group. These events will also be summarized by other categories specified in the endpoints (e.g., time of onset, number of days of occurrence, action taken).

Unsolicited AEs will be collected, coded, and summarized by MedDRA system organ class (SOC) and PT. For each unsolicited AE, the number of subjects with at least one instance of that event will be reported. Unsolicited AEs will also be tabulated by intensity and relatedness of study vaccine and by other categories specified in the endpoints.

Immediate reactions, SAEs, and any event that leads to subject withdrawal from the study will be tabulated separately.

5.2 Analysis Sets

Four analysis sets will be used: The Full Analysis Set (FAS), the Full Analysis Set for persistence (FASP), the Per-Protocol Analysis Set (PPAS), and the Safety Analysis Set (SafAS).

5.2.1 Full Analysis Set

Full Analysis Set

The FAS is defined as the subset of subjects who received at least 1 dose of the study vaccine and had a valid post-vaccination blood sample result.

Full Analysis Set for Persistence

The FASP is defined as a subset of subjects who had a valid pre-vaccination blood sample result.

5.2.2 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was planned to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
- Subject did not provide the post-dose serology sample at Visit 2 in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy / medication / vaccine
- Subject had another protocol deviations that affected the subject's immune response, as determined by the clinical team before locking the database

In addition to the reasons listed above, subjects will also be excluded from the PPAS if their post-vaccination serology sample did not produce a valid test result (i.e., results for all antigens are missing).

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

5.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one dose of the study vaccine[a] and have any safety data available. All subjects 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).

[a] for which safety data are scheduled to be collected

5.2.4 Other Analysis Sets

Enrolled subjects

Enrolled subjects are subjects for whom a CRF has been created.

5.2.5 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS. Immune persistence analyses will be performed on the FASP. All safety analyses will be performed on the SafAS. All analyses will be based on the overall study population as well as the type of meningococcal vaccine received in MET54 (subjects who received MenACYW conjugate vaccine and subjects who received Nimenrix® 3 years earlier as toddlers).

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

No replacement will be done. In all subject listings, partial and missing data will be clearly indicated as missing.

5.3.1.1 Immediate

For unsolicited non-serious 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.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will remain missing and not be imputed. Such SAEs will not be considered as immediate.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop 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 visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.1.6 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

Missing data will not be imputed. No test or search for outliers will be performed.

In order to appropriately manage extreme values (undetectable responses < LLOQ and ≥ upper limit of quantitation [ULOQ]), the computational rule described in section 4.4.2.1 is applied to the values provided in the clinical database for each blood sample drawn for analysis purposes.

The derived endpoint of fold-rise is computed as described in Section 4.4.2.3 for extreme values, to minimize the numerator and maximizes the denominator

5.3.3 Efficacy

Not applicable

5.4 Interim / Preliminary Analysis

No planned interim / preliminary analyses were performed.

5.5 Determination of Sample Size and Power Calculation

No sample size calculations were performed. This is an exploratory study with no hypothesis-driven primary objectives. All available subjects who participated in and completed the MET54 study and received either MenACYW conjugate vaccine or Nimenrix® vaccine, as a part of the study, were to be enrolled.

5.6 Data Review for Statistical Purposes

A review of the data has been anticipated through the data review process led by Data Management before database lock. This review of the data included a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

The analysis set FASP is added in the SAP. FASP will be used to describe the immune persistence 3 years after primary vaccination with either MenACYW conjugate vaccine or Nimenrix®.

No other significant change occurred during the conduct of the trial not documented in a protocol amendment.

6 References List

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5. The European Meningococcal Disease Society (EMGM). 11th EMGM Meeting, 18-20 May 2011. Ljubljana Slovenia. Poster P035, 037-040.
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