Statistical Analysis Plan

MenACWY-TT-101 (C0921005)

Detailed Title:	A phase IIIb, open study to evaluate the immunogenicity, reactogenicity and safety of a booster dose of MenACWY-TT vaccine administered 10 years after healthy subjects aged 11-17 years received either MenACWY-TT vaccine (Nimenrix®) or Mencevax® ACWY.
SAP version:	Version 1
SAP date:	31-Aug-2017
Scope:	All data pertaining to the above study.
Coordinating author:	PPD
Other author(s):	PPD
Ad hoc reviewers:	PPD

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ACWY-TT	vaccinated with MenACWY-TT in Study MenACWY-TT-036
ANOVA	analysis of variance
ATP	according-to-protocol
CI	confidence interval
CSR	clinical study report
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
GSK	GlaxoSmithKline
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*N meningitidis* group A
MenACWY-TT	meningococcal group ACWY tetanus toxoid conjugate
MenC	*N meningitidis* group C
Mencevax® ACWY	meningococcal groups ACWY plain polysaccharide vaccine
MenPS	vaccinated with Mencevax ACWY in Study MenACWY-TT-036
MenW-135	*N meningitidis* group W-135
MenY	*N meningitidis* group Y
NOCI	new-onset chronic illness
PHE	Public Health England
RCDC	reverse cumulative distribution curve
rSBA	serum bactericidal assay using rabbit complement
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TT	tetanus toxoid
TVC	total vaccinated cohort

1. VERSION HISTORY

This statistical analysis plan (SAP) for Study C0921005 (also known as MenACWY-TT-101 EXT 036: Y10) is based on protocol Amendment 3 dated 12 July 2017.

Table 1. Summary of Major Changes in SAP Amendments

Date	Description	Protocol Version
31-Aug-2017	Version 1	Amendment 3, 12 Jul 2017

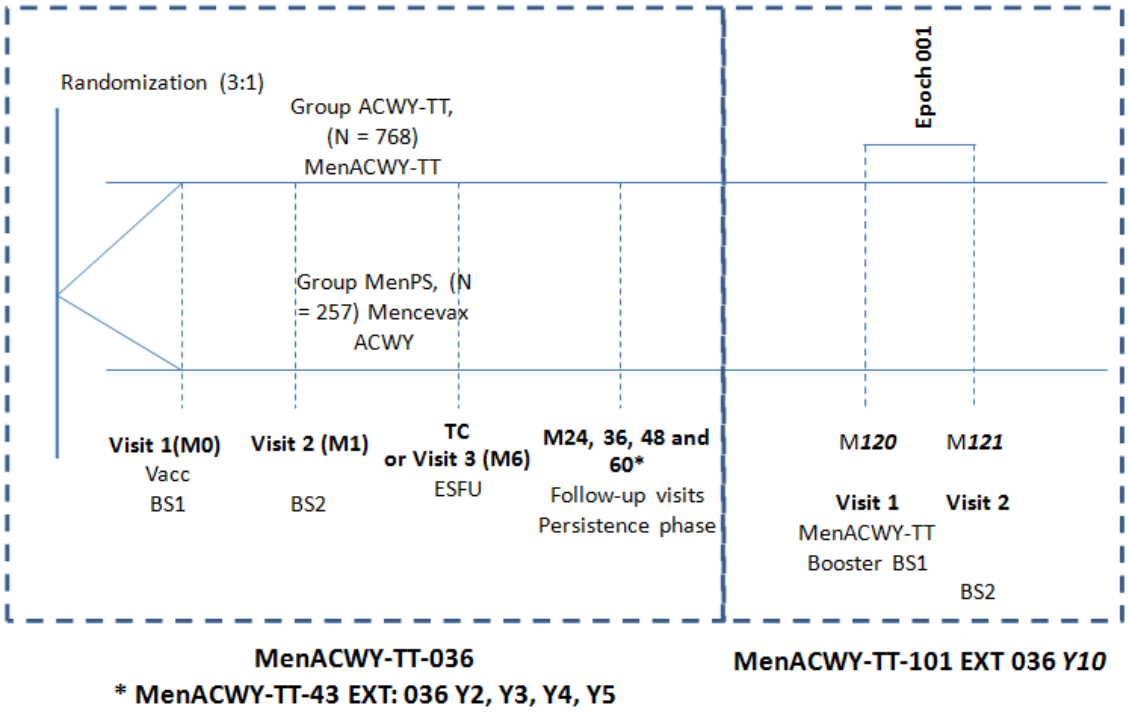
2. INTRODUCTION

Subjects aged 11-17 years were vaccinated with 1 dose of either meningococcal group ACWY tetanus toxoid conjugate (MenACWY-TT) or Mencevax® ACWY in Study MenACWY-TT-036. The participants were further followed for the assessment of persistence in Study MenACWY-TT-043, and unless they withdrew their consent, they were invited for a yearly blood sample, regardless of their serostatus at the previous persistence time point, from Year 2 to Year 5 after primary vaccination. Five years after vaccination, the percentage of subjects with serum bactericidal assay using rabbit complement (rSBA) titers ≥1:8 ranged between 86.0%-97.5% in the subjects vaccinated with Nimenrix® and between 34.9%-93.0% in the subjects vaccinated with Mencevax ACWY.

The purpose of this study is to evaluate the safety and immunogenicity of a booster dose of MenACWY-TT vaccine administered 10 years after healthy subjects aged 11-17 years received either a single dose of meningococcal group ACWY tetanus toxoid conjugate (MenACWY-TT) vaccine or Mencevax ACWY. Study MenACWY-TT-036 was conducted in India, the Philippines and Taiwan. The MenACWY-TT-043 persistence study up to Year 5 after primary vaccination included only India and the Philippines. Due to Good Clinical Practice (GCP) issues in India, this booster study will only be conducted in the Philippines.

This SAP provides the detailed methodology for summaries and statistical analyses of the booster data collected in Study C0921005. Statistical analyses of persistence up to Month 120 are also described. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Design



M = month
BS = blood sample
Vacc = vaccination
TC = telephone contact
ESFU = extended safety follow-up
N = number of subjects in the primary total vaccinated cohort

Subjects aged 11-17 years were randomized to either MenACWY-TT (ACWY-TT) or Mencevax ACWY (MenPS) in primary study MenACWY-TT-036. Blood samples were obtained 1 month after vaccination. Subsequent blood samples were obtained at Months 24, 36, 48, and 60 in order to assess persistence of meningococcal antibodies. Immunogenicity after the initial vaccination was analyzed in the clinical study report (CSR) for Study MenACWY-TT-036. Persistence was analyzed in annual study reports for Study MenACWY-TT-043 Y2, Y3, Y4 and Y5.

Subjects will receive a booster vaccination at Month 120 in this study. The booster vaccine will be MenACWY-TT for each subject. Blood samples will be obtained before booster vaccination (Month 120) and 1 month after vaccination (Month 121). Titers before and after the booster dose will be used to assess response to booster vaccination. The vaccine groups will be ACWY-TT and MenPS, corresponding to the initial vaccination, even though all subjects will receive MenACWY-TT as the booster vaccine at Month 120.

2.2. Study Objectives

Study objectives are described in terms of antibody titers to *N meningitidis* group A (MenA), *N meningitidis* group C (MenC), *N meningitidis* group W-135 (MenW-135), and *N meningitidis* group Y (MenY). Titers will be measured with a serum bactericidal assay using rabbit complement (rSBA).

2.2.1. Primary Objective

One month after the booster vaccination with MenACWY-TT:

- Evaluate the immunogenicity of a booster dose of MenACWY-TT conjugate vaccine in terms of the percentage of subjects with an rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY booster response*.

  *Booster response to meningococcal antigens (A, C, W-135 and Y) is defined as:

  - For initially seronegative subjects (prevaccination rSBA titer <1:8): rSBA antibody titer ≥1:32 1 month after vaccination, and

  - For initially seropositive subjects (prevaccination rSBA titer ≥1:8): at least 4-fold increase in rSBA titer from prevaccination to 1 month after vaccination.

2.2.2. Secondary Objectives

Secondary immunogenicity objectives:

One month post-booster vaccination with MenACWY-TT vaccine:

- Evaluate the immunogenicity of a booster dose of MenACWY-TT conjugate vaccine with respect to the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers ≥1:8, ≥1:128 and geometric mean titers (GMTs).

Before the booster vaccination and 1 month after the booster vaccination with MenACWY-TT vaccine:

- Evaluate the percentage of subjects with anti-tetanus toxoid (TT) concentrations ≥0.1 IU/mL, ≥1.0 IU/mL and geometric mean concentrations (GMCs).

Long-term persistence phase 10 years after primary vaccination with MenACWY-TT or Mencevax ACWY in Study MenACWY-TT-036:

- Evaluate the long-term antibody persistence induced by MenACWY-TT conjugate vaccine as compared to Mencevax ACWY when administered to individuals 11-17 years

of age with respect to the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers ≥1:8, ≥1:128 and GMTs.

Secondary safety objectives:

- Evaluate the safety and reactogenicity of a booster dose of the MenACWY-TT conjugate vaccine.
- Describe serious adverse events (SAEs) related to study vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in Study MenACWY-TT-036 or in Study MenACWY-TT-043 EXT:036 Y2, 3, 4, 5.*

  *last visit in Study MenACWY-TT-036 will only be considered for subjects who did not participate in Study MenACWY-TT-043 EXT:036 Y2, 3, 4, 5.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

Immunogenicity with respect to the components of the investigational vaccine 1 month after booster vaccination with MenACWY-TT vaccine:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY booster response*.

  *Booster response to meningococcal antigens (A, C, W-135 and Y) is defined as:

  – For initially seronegative subjects (prevaccination rSBA titer <1:8): rSBA antibody titer ≥1:32 one month after vaccination, and

  – For initially seropositive subjects (prevaccination rSBA titer ≥1:8): at least 4-fold increase in rSBA titers from prevaccination to 1 month after vaccination.

3.2. Secondary Endpoints

Immunogenicity

Immunogenicity with respect to the components of the investigational vaccine before and 1 month after booster vaccination with MenACWY-TT vaccine:

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titers ≥1:8, ≥1:128, and GMTs.
- Percentage of subjects with anti-TT concentrations ≥0.1 IU/mL, ≥1.0 IU/mL, and GMCs.

Safety and reactogenicity

- Occurrence of solicited local and general events within 4 days (Day 0 to Day 3) after MenACWY-TT booster vaccination.

- Occurrence of unsolicited adverse events (AEs), within 31 days (Day 0 to Day 30) after MenACWY-TT booster vaccination.

- Occurrence of SAEs, Guillain-Barré syndrome (GBS) and new-onset chronic illnesses (NOCIs) (eg, asthma, autoimmune disorders, type I diabetes, allergies) within 31 days (Day 0 to Day 30) after MenACWY-TT booster vaccination.

- Occurrence of SAEs related to primary vaccination and any event related to lack of vaccine efficacy (ie, meningococcal disease) from the subject's last visit in the primary study MenACWY-TT-036 or in the persistence study MenACWY-TT-043 EXT:036 Y2, 3, 4, 5 until entry in Study C0921005 (MenACWY-TT-101 EXT:036 Y10).

The intensity of the solicited events will be assessed as described in Table 2:

Table 2. Intensity Scales for Solicited Events

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

* Fever is defined as temperature ≥37.5°C for oral, axillary or tympanic route, or ≥38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be graded as follows:

Grade	Intensity
0	None
1	>0 - ≤20 mm
2	>20 - ≤50 mm
3	>50 mm

The maximum intensity of fever from the oral/axillary or tympanic routes will be graded as follows:

Grade	Intensity
0	<37.5°C
1	≥37.5°C - ≤38.5°C
2	>38.5°C - ≤39.5°C
3	>39.5°C

Temperatures obtained via the rectal route will be adjusted to the same scale by subtracting 0.5°C.

Subjects will be summarized by the maximum intensity over Days 0-3.

The intensity of the unsolicited AEs will be assessed as described below:

1 (mild) = an AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = an AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = an AE which prevents normal, everyday activities. Such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AE (including SAE).

Each solicited event and unsolicited AE will have an assigned causality:

All solicited local (injection site) events will be considered causally related to vaccination. The investigator is obligated to assess the relationship between investigational

vaccine/product and the occurrence of each unsolicited AE (including SAE) and for general solicited events.

3.3. Baseline Variables

Baseline variables will include sex, race, age at primary vaccination, age at booster vaccination, and elapsed years from primary vaccination to booster vaccination. Elapsed years will be calculated as [date of booster vaccination minus date of primary vaccination + 1]/365.25, rounded down to the nearest tenth decimal place.

4. STUDY POPULATION

4.1. Booster Total Vaccinated Cohort (TVC)

The booster TVC for safety will include all vaccinated subjects in Study MenACWY-TT-036 with a MenACWY-TT booster vaccine administration documented.

For the analysis of immunogenicity after the booster vaccination the booster TVC will include all subjects for whom data concerning immunogenicity endpoint measures after the booster vaccination are available.

4.2. Booster According-to-Protocol (ATP) Cohort for Safety

The booster ATP cohort for safety will include all subjects:

- who meet all inclusion criteria and no exclusion criteria for the study.
- who received a dose of study vaccine MenACWY-TT or Mencevax ACWY in Study MenACWY-TT-036.
- who received a MenACWY-TT booster dose.
- who had a known administration site for the booster vaccine.
- who did not receive a vaccine not specified or forbidden in the protocol (subjects who received a vaccine not foreseen by the study protocol 30 days after the study vaccine dose will be eliminated from the booster ATP cohort for safety if the vaccine not foreseen by the protocol was administered before the postvaccination blood sample).
- who were not excluded from the ATP cohort for persistence at Month 120, unless the reason for exclusion was either noncompliance with the protocol-defined serum sampling windows or a lack of availability of immunogenicity results at Month 120 (prebooster vaccination).

No analyses using the booster ATP cohort for safety are proposed. However, this cohort helps define the booster ATP cohort for immunogenicity.

4.3. Booster ATP Cohort for Immunogenicity

The booster ATP cohort for immunogenicity will include subjects:

- who meet requirements of the booster ATP cohort for safety.
- who comply with procedures defined in the protocol including meeting visit interval from primary vaccination in Study MenACWY-TT-036 to booster vaccination: 520 ±26 weeks, inclusive.
- who comply with procedures defined in the protocol including meeting blood sampling intervals from Visit 1 to Visit 2: 21-48 days, inclusive.
- who have assay results available for antibodies against any study vaccine antigen for the blood sample taken 1 month after booster vaccination at Month 121, and
- who were not administered a vaccine not foreseen by the study protocol before the post–booster vaccination blood sample. Other restrictions may apply (see Section 4.6).

4.4. Total Cohort at Month 120

The total cohort at Month 120 will include all vaccinated subjects from the vaccination stage of Study MenACWY-TT-036 who return for the Month 120 follow-up, ie, subjects who were vaccinated in MenACWY-TT-036 and returned for Month 120 visit.

For the analysis of persistence, the total cohort at the Month 120 visit will be further restricted to vaccinated subjects for whom data concerning persistence endpoint measures are available, ie, at least 1 titer at Month 120 visit.

4.5. ATP Cohort for Persistence at Month 120

The ATP cohort for antibody persistence for the Month 120 visit will include all evaluable subjects:

- who were eligible in Study MenACWY-TT-036.
- who received the primary vaccination with MenACWY-TT or Mencevax ACWY during Study MenACWY-TT-036.
- who had assay results for at least one tested antigen at Month 120.
- who did not receive a meningococcal vaccine not planned in Study MenACWY-TT-036 before Month 120 visit.

- who did not have a history of meningococcal group A, C, W-135, or Y disease prior to Month 120 visit.

- who complied with the blood sampling interval (520 ±26 weeks, inclusive from primary vaccination in Study MenACWY-TT-036 at Month 120).

- who did not have an immunocompromising medical condition.

- who did not receive any immunosuppressant(s) or other immune-modifying drug(s), immunoglobulins, any blood products, investigational drugs, and/or investigational vaccines during the timeframe specified in the protocol.

- who were not excluded from the ATP cohort for immunogenicity in the primary Study MenACWY-TT-036, and/or from the previous ATP persistence cohorts, unless the reason for exclusion was either noncompliance with the protocol-defined serum sampling windows or a lack of availability of immunogenicity results at previous time point.

Other restrictions may apply (see Section 4.6).

4.6. Possible Additional Restrictions on Booster ATP for Immunogenicity and ATP for Persistence at Month 120

The use of concomitant medications/products/vaccines discussed in Section 6.5.2 of the protocol may also exclude a subject from the booster ATP cohort for immunogenicity. The use of the following concomitant medications/products/vaccines may determine a subject's inclusion in the ATP analysis.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.

- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day with an upper limit of 10 mg/day or equivalent. Inhaled, topical, and intra-articular steroids are allowed.

- A vaccine not allowed by the study protocol but administered during the period starting 30 days before the booster dose of vaccine and ending 30 days after, with the exception of inactivated influenza vaccine which can be administered at any time during the study according to the local recommendations.

- Administration of a meningococcal vaccine not allowed by the study protocol at any time during the study period.

- Immunoglobulins and/or any blood products administered within the 3 months preceding the study vaccination or planned administration during the study (ie, between Visit 1 and Visit 2).

The following intercurrent medical conditions may result in the elimination of subjects from the ATP cohort for immunogenicity:

- Occurrence of meningococcal disease.
- Any confirmed or suspected condition that has the capability of altering the subject's immune response (eg, intercurrent lymphopenia).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).

A detailed, comprehensive list of reasons for elimination from ATP analyses will be established at the time of data cleaning.

4.7. Adapted ATP Cohort

The adapted ATP cohort will denote, for each time point, subjects belonging to the corresponding ATP cohort for immunogenicity (Month 0 and Month 1) or persistence (all other months) for that time point.

The blood sampling intervals are 21 to 48 days for Month 1; 96 to 112 weeks for Month 24; 148 to 164 weeks for Month 36; 200 to 216 weeks for Month 48; 252 to 268 weeks for Month 60; and 494 to 546 weeks for Month 120.

The adapted ATP cohort will be used for the modeling prediction analysis (Section 5.2.3).

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. General Methods

All confidence intervals (CIs) for proportions will be 2-sided 95% intervals, obtained using the exact Clopper-Pearson method, as described by Agresti.[1]

The standardized asymptotic 95% CI for the difference in proportions will use the Miettinen and Nurminen method, which is described by Miettinen and Nurminen[2] and by Newcombe.[3]

The following decimal description will be used for the demography, reactogenicity, immunogenicity, and persistence analyses.

Table 3. Description of Parameters

Display Table	Parameters	Number of Decimal Digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
rSBA-MenA	GMT	1
rSBA-MenC	GMT	1
rSBA-MenW-135	GMT	1
rSBA-MenY	GMT	1
Immunogenicity	Ratio of GMT	2
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

Abbreviations: GMT = geometric mean titer; LL = lower limit of the confidence interval; rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; UL = upper limit of the confidence interval.

5.2. Methods for Immunogenicity

GMTs and GMCs will be obtained by log transformations of indicated values, averaging the log values, then exponentiating the result. The 2-sided 95% CI will be obtained by calculating the CI in log scale, referencing the t-distribution, and then exponentiating the lower and upper limits.

The day of booster vaccination will be labeled Day 0.

5.2.1. Within Group Immunogenicity Methods

For each group, at each blood sampling time point (Month 120 and Month 121), for each antigen assessed:

- Percentage of subjects with rSBA booster response with 95% CIs will be calculated.
- GMTs/GMCs with 95% CIs will be tabulated.
- Percentages of subjects with titers/concentrations above proposed cutoffs and with 95% CIs will be calculated.
- The antibody titers/concentrations will be tabulated and also presented using reverse cumulative distribution curves.

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5.3. Methods for Solicited Events and Unsolicited AEs

5.3.1. Solicited Local And General Events (Within 4 Days Of Vaccination)

Solicited local and general events from Days 0-3 will be recorded on diary cards.

The percentage of subjects reporting each individual solicited local (any grade, Grade 3, medical advice) and general (any grade, Grade 3, related, Grade 3 and related, medical advice) event during the 4-day follow-up period (Days 0-3) after vaccination and its exact 95% CI will be tabulated. Occurrence of fever will also be reported per temperature Grade 0,1, 2, and 3 as well as the percentage of subjects with oral temperature reported by cumulative 0.5°C increment.

The proportions of subjects reporting injection site redness >50 mm and the proportions of subjects reporting injection site swelling >50 mm will also be compiled.

Per Section 8.2.3 of the protocol, "Fever is defined as temperature ≥37.5°C for oral, axillary or tympanic route, or ≥38.0°C for rectal route. The preferred route for recording temperature in this study will be oral".

5.3.2. Solicited Events and Unsolicited AEs (Within 4 Days of Vaccination)

The percentage of subjects with at least 1 local event (solicited event and unsolicited AE), with at least 1 general event (solicited event and unsolicited AE), and with any event (solicited and unsolicited) during the 4-day (Days 0-3) follow-up period will be tabulated with exact 95% CI.

5.3.3. Unsolicited AEs (Within 31 Days Of Vaccination)

The percentage of subjects with unsolicited AEs within 31 days after booster vaccination (Days 0-30) and the exact 95% CI will be tabulated by vaccine group and by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited AEs, for unsolicited AEs possibly related to vaccination, and for Grade 3 unsolicited AEs possibly related to vaccination. For any given unsolicited AEs, the unrestricted, Grade 3, and related AEs analyses will use the same tier methodology.

SAEs (including cases of meningococcal disease and GBS) and NOCIs within 31 days following the booster vaccination will be assessed with exact 95% CI.

Pregnancies occurring within 31 days following the booster vaccination will be listed, as well as AEs/SAEs leading to withdrawal, SAEs related to study vaccination or any event related to lack of vaccine efficacy, and SAEs related to study participation.

5.3.4. Unsolicited SAEs

The percentage of subjects with SAEs related to primary vaccination and any event related to lack of vaccine efficacy from the subject's last visit in the primary study MenACWY-TT-036 or in the persistence study MenACWY-TT-043 EXT:036 Y2, 3, 4, 5 until entry in Study C0921005 (MenACWY-TT-101 EXT:036 Y10) and the exact 95% CI will be tabulated by vaccine group.

5.4. Methods for Baseline Characteristics

Summary statistics will be compiled for sex, race, age at booster vaccination, age at primary vaccination, and elapsed years from primary vaccination to booster vaccination. Sex and race will be summarized with frequency counts. Ages and elapsed years will be summarized by sample size, mean, standard deviation, minimum, and maximum. No statistical tests will be performed. Subject date of birth, sex, and race information were captured in primary study MenACWY-TT-036 database.

Frequency counts and proportions will be compiled by vaccine group for number of subjects returning at Month 120 visit, number of subjects receiving booster vaccination, number of subjects completed, and number of subjects withdrawn. The reasons for withdrawal will also be summarized.

The vaccine group sample sizes for the total cohort at Month 120 will be reconciled to the sample sizes for the ATP cohort for persistence at Month 120 by:

- Tabulating sample sizes for total cohort at Month 120.
- Tabulating sample sizes for ATP cohort for persistence at Month 120.
- Tabulating the sample sizes of reasons that subjects who are in total cohort are excluded from ATP cohort.

The vaccine group sample sizes for the booster TVC cohort will be reconciled to the booster ATP cohort for safety in the same way. The vaccine group sample sizes for the booster ATP cohort for safety will then be reconciled to the booster ATP cohort for immunogenicity.

Demographics summary will be generated on ATP cohort for persistence at Month 120, booster TVC cohort and Booster ATP cohort for immunogenicity.

5.5. Methods to Manage Missing Data

5.5.1. Immunogenicity

Missing immunogenicity data will be retained as missing. Meningococcal antibody titers and tetanus toxoid antibody concentrations below the cutoff will be set to 0.5*cutoff before performing GMT/GMC calculations. The cutoff for each of the 4 meningococcal rSBAs is 1:8. The cutoff for the tetanus assay is 0.1 IU/mL.

Titers from blood samples exposed to temperature excursions may be excluded from the analysis. Determinations of exclusions will be on a case-by-case basis.

5.5.2. Safety

A subject will be considered missing for any given solicited local or general event within Days 0-3 only if the subject does not record any values, either ‘yes’ or ‘no’, for the indicated solicited event. If the subject has at least one nonmissing response on at least one day, then the subject will be considered nonmissing for that solicited event.

Subjects with at least 1 unsolicited AE, or with completion date on Day 0 or later, will be eligible for AE analysis.

No missing safety data will be imputed.

6. ANALYSES AND SUMMARIES

This section specifies which endpoints will be analyzed for which cohorts.

6.1. Immunogenicity Endpoints

6.1.1. Primary Endpoints

The primary endpoint is the booster vaccination response. The primary analysis for this endpoint will use the booster ATP cohort for immunogenicity. For any group, if more than 5% of subjects who have serological results are excluded from the Booster ATP cohort, a second analysis based on the booster TVC will be performed as a sensitivity analysis. Proportions and their 2-sided 95% CIs will be compiled for each meningococcal group.

Table 4. Primary Endpoint Analyses

Endpoint	Cohort	Statistical Method/Test
Booster response	Booster ATP cohort for immunogenicity	2-sided exact 95% CI on each proportion
Booster response	Booster TVC	2-sided exact 95% CI on each proportion

Abbreviations: ATP = according to protocol; TVC = total vaccinated cohort.

6.1.2. Secondary Endpoints

The secondary endpoints are proportions of subjects achieving indicated meningococcal or tetanus antibody level cutoffs. Both prebooster and postbooster results will be analyzed. Geometric means and their 2-sided 95% CIs will also be compiled for all groups at both prebooster and postbooster visits.

Table 5. Secondary Endpoint Analyses in Booster ATP Cohort for Immunogenicity

Endpoint	Cohort	Statistical Method/Test
Proportion of subjects with rSBA titers ≥1:8 for each meningococcal group, both before and after booster vaccination	Booster ATP cohort for immunogenicity	2-sided exact 95% CI on each proportion
Proportion of subjects with rSBA titers ≥1:128 for each meningococcal group, both before and after booster vaccination	Booster ATP cohort for immunogenicity	2-sided exact 95% CI on each proportion
Proportion of subjects with anti-TT concentrations ≥0.1 IU/mL, both before and after booster vaccination	Booster ATP cohort for immunogenicity	2-sided exact 95% CI on each proportion
Proportion of subjects with anti-TT concentrations ≥1.0 IU/mL, both before and after booster vaccination	Booster ATP cohort for immunogenicity	2-sided exact 95% CI on each proportion
GMT and 95% CI for each meningococcal group, both before and after booster vaccination	Booster ATP cohort for immunogenicity	2-sided exact 95% CI on each geometric mean
GMC and 95% CI for TT antibody concentration, both before and after booster vaccination	Booster ATP cohort for immunogenicity	2-sided exact 95% CI on each geometric mean
Tabulation of percentage of subjects with rSBA titers <1:8, ≥1:8, ≥1:16, ≥1:32, etc. for each meningococcal group	Booster ATP cohort for immunogenicity	Incidence proportions

Abbreviations: ATP = according to protocol; GMT = geometric mean titer; rSBA = serum bactericidal assay using rabbit complement; TT = tetanus toxoid.

If more than 5% of the subjects from either vaccine group who have serological results are excluded from the booster ATP cohort for immunogenicity, then the secondary endpoints (Table 5) will be re-analyzed using the booster TVC.

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6.1.4. Figures

Reverse cumulative distribution curves (RCDCs) will be constructed for pre- and postbooster immunogenicity values. Separate figures will be compiled for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY, and anti-TT. Each figure will include pre- and postbooster curves for ACWY-TT and MenPS groups. The cohort will be the booster ATP cohort for immunogenicity.

6.1.5. Persistence Analyses

The persistence analyses will consist of 3 parts.

1. Descriptive statistics (percentage of subjects with titers ≥1:8, percentage of subjects with titers ≥1:128, GMT) for each time point from Month 0, Month 1, and Month 120. The cohort will be the ATP cohort for persistence at Month 120.

Tetanus toxoid antibody concentrations will not be included in the persistence analyses.

For any group, if more than 5% of subjects who have serological results are excluded from the ATP cohort for persistence at Month 120, a second analysis based on the total cohort at Month 120 will be performed to complement the ATP analysis.

Table 7. Persistence Analyses

Endpoint	Cohort	Statistical Method/Test
Proportion of subjects with rSBA titers ≥1:8 for each meningococcal group at Month 120	ATP cohort for persistence at Month 120	2-sided exact 95% CI for proportion within each group; 2-sided standardized asymptotic 95% CI for the difference of proportions between ACWY-TT and MenPS groups
Proportion of subjects with rSBA titers ≥1:128 for each meningococcal group at Month 120	ATP cohort for persistence at Month 120	2-sided exact 95% CI for proportion within each group; 2-sided standardized asymptotic 95% CI for the difference of proportions between ACWY-TT and MenPS groups
Ratio of GMTs between ACWY-TT and MenPS for each meningococcal group at Month 120	ATP cohort for persistence at Month 120	ANOVA*
Tabulation of percentage of subjects with rSBA titers <1:8, ≥1:8, ≥1:16, ≥1:32, etc. for each meningococcal group at Month 120	ATP cohort for persistence at Month 120	Incidence proportions
CCI [redacted]		

Abbreviations: ANOVA = analysis of variance; ATP = according to protocol; GMT = geometric mean titer; rSBA = serum bactericidal assay using rabbit complement.
* Vaccine group as fixed effect in ANOVA model.

6.2. Safety and Reactogenicity

Safety tables will contain proportion for ACWY-TT group (and 95% CI) and proportion for MenPS group (and 95% CI), except where indicated.

6.2.1. Solicited Local Events

The analyses of solicited local events will include compilations of the proportion of reactions as well as estimating the difference between vaccine groups in proportions (Table 8).

Table 8. Summary of Analyses for Solicited Local Events for Days 0-3 (4 Days) After Booster Vaccination

Endpoint	Cohort	Statistical Method/Test
Pain, redness, and swelling (all) Grade 3 for pain, >50 mm for redness, >50 mm for swelling Medical advice for pain, redness, and swelling	Booster TVC	2-sided exact 95% CI on each proportion

Abbreviations: ATP = according to protocol; TVC = total vaccinated cohort.

Large injection site reactions after MenACWY-TT booster vaccination will be described in detail.

6.2.2. Solicited General Events

The analyses of solicited general events will include compilations of the proportions of events as well as 95% CI from exact test in each group (Table 9).

Occurrence of fever will also be reported per oral temperature Grade 0, 1, 2, and 3 as well as the percentage of subjects with oral temperature reported by cumulative 0.5°C increment.

Table 9. Summary of Analyses for Solicited General Events Days 0-3 (4 Days) After Booster Vaccination

Endpoint	Cohort	Statistical Method/Test
Fever, gastrointestinal symptoms, headache, and fatigue (all) Fever ≥37.5°C, >38.0°C, >38.5°C, >39.0°C, >39.5°C Fever <37.5°C (Grade 0), ≥37.5°C - ≤38.5°C (Grade 1), >38.5°C - ≤39.5°C (Grade 2), and >39.5°C (Grade 3) Fever >39.5°C, Grade 3 for gastrointestinal symptoms, headache, and fatigue Related fever, gastrointestinal symptoms, headache, and fatigue Related fever >39.5°C, related Grade 3 gastrointestinal symptoms, headache, and fatigue Medical advice for fever, gastrointestinal symptoms, headache, and fatigue	Booster TVC	2-sided exact 95% CI on each proportion

Abbreviation: TVC = total vaccinated cohort.
Note: when temperature is measured by the rectal route, the corresponding oral temperature will be derived by subtracting 0.5°C from the temperature recorded.

6.2.3. Solicited Events and Unsolicited AEs Combined Days 0-3

The proportion of subjects with at least 1 event (solicited and unsolicited), with at least 1 local event (solicited event and unsolicited AE), and with at least 1 general event (solicited event and unsolicited AE) during the 4-day (Days 0-3) period following the booster vaccination will be tabulated. Proportions and 2-sided 95% CI's will also be obtained for Grade 3 events. Only the booster TVC cohort will be analyzed (Table 10).

Table 10. Summary of Solicited Events and Unsolicited AEs, During the 4-Day (Days 0-3) Period After Booster Vaccination

Endpoint	Cohort	Statistical Method/Test
At least 1 event (solicited event and/or unsolicited AE), or at least 1 local event (solicited local event and/or unsolicited local AE), or at least 1 general event (solicited general event and/or unsolicited general AE),	Booster TVC	2-sided exact 95% CI on each proportion
At least 1 Grade 3 event, at least 1 Grade 3 local event, at least 1 Grade 3 general event	Booster TVC	2-sided exact 95% CI on proportions
At least 1 related event, at least 1 related local event, at least 1 related general event	Booster TVC	2-sided exact 95% CI on proportions

Abbreviations: PT = preferred term; SOC = system order class; TVC = total vaccinated cohort.

6.2.4. Unsolicited AEs

AE output will be sorted alphabetically by MedDRA preferred term within SOC. The proportion of subjects with at least one unsolicited AE and the exact 95% CIs will be compiled. Compilations will be performed for AEs, Grade 3 AEs, related AEs, and related and Grade 3 AEs within 31 days after vaccination (Days 0-30). The number and percentage of subjects who experienced SAE and new onset of chronic illness within 31 days following booster vaccination will be tabulated with exact 95% CI. (Table 11).

Table 11. Summary of Analyses for Unsolicited AEs Days 0-30 (31 Days) After Booster Vaccination

Endpoint	Cohort	Statistical Method/Test
All AEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
Grade 3 AEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
Related AEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
Related and Grade 3 AEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
All SAEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
Related SAEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
Fatal SAEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
Related Fatal SAEs by SOC and PT	Booster TVC	2-sided exact 95% CI on proportions
NOCI with PTs in SOC	Booster TVC	2-sided exact 95% CI on proportions

Abbreviations: NOCI = new-onset chronic illness; PT = preferred term; SOC = system organ class; TVC = total vaccinated cohort.

Pregnancies occurring within 31 days (Day 0 to Day 30) after MenACWY-TT booster vaccination will be listed.

6.2.5. SAEs Reported Before Booster Vaccination

SAEs related to the primary study MenACWY-TT-036 vaccination and any event related to lack of vaccine efficacy (ie, meningococcal disease) will be compiled. Only SAEs from the last visit in MenACWY-TT-036 or MenACWY-TT-043, whichever is later, until entry in this study will be included. The cohort will be the total cohort at Month 120.

Table 12. Summary of SAEs Since Last MenACWY-TT-036 Visit or MenACWY-TT-043 Visit Up to the Booster Vaccination

Endpoint	Cohort	Statistical Method/Test
SAEs by SOC and PT	Total cohort at Month 120 visit	2-sided exact 95% CI on proportions

Abbreviation: SOC = system organ class.

6.2.6. Concomitant Medications

The percentage of subjects using concomitant medication (any medication, any antipyretic/analgesic, or any antipyretic/analgesic taken prophylactically) during the 4-day and 31-day follow-up periods (Days 0-3 and Days 0-30, respectively) after booster vaccination will be summarized. The cohort will be the booster TVC. Analyses are summarized in Table 13.

Table 13. Summary of Analyses for Concomitant Medications

Endpoint	Cohort	Statistical Method/Test
Any concomitant medication, any antipyretic/analgesic, any antipyretic/analgesic taken prophylactically Days 0-3	Booster TVC	2-sided exact 95% CI on proportions
Any concomitant medication, any antipyretic/analgesic, any antipyretic/analgesic taken prophylactically Days 0-30	Booster TVC	2-sided exact 95% CI on proportions

Abbreviation: TVC = total vaccinated cohort.

6.3. Subset Analyses

Not applicable.

6.4. Baseline and Other Summaries and Analyses

The descriptive summary for sex, race, and age will be presented by total cohort Month 120, ATP cohort for persistence at Month 120, booster TVC, and booster ATP cohort for immunogenicity populations. Subject's date of birth, sex, and race information will be from primary study MenACWY-TT-036 or MenACWY-TT-043.

The analyses for study conduct and subject disposition are presented below:

- Number of subjects with booster vaccination, number of subjects completed study, and number of subjects withdrawn in total cohort at Month 120.
- Number of subjects in total cohort at Month 120, number of subjects in ATP cohort for persistence at Month 120, and number of subjects with reason(s) for exclusion from ATP cohort for persistence at Month 120.
- Number of subjects in booster TVC, number of subjects in booster ATP cohort for safety, number of subjects with reason(s) for exclusion from booster ATP cohort for safety, number of subjects in booster ATP cohort for immunogenicity, and number of subjects with reason(s) for exclusion from booster ATP cohort for immunogenicity.
- Number and proportion of subjects returning diary cards in booster TVC.

7. INTERIM ANALYSES

Not applicable.

8. REFERENCES

1. Agresti, A. "Exact Small-Sample Inference." In *Categorical Data Analysis. 2nd Ed.*, 18-20. Hoboken, NJ: John Wiley & Sons, Inc, 2002.

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