

Statistical Analysis Plan



MenACWY-TT-099 (C0921002)

Detailed Title:	A phase IIIb, open, multi-center study to evaluate the long-term antibody persistence at 6, 7, 8, 9 and 10 years after the administration of one dose of meningococcal conjugate vaccine MenACWY-TT versus one dose of meningococcal polysaccharide vaccine Mencevax ACWY, and to evaluate the safety and immunogenicity of a booster dose of MenACWY-TT vaccine administered 10 years after primary vaccination of 11-55 year old subjects with MenACWY-TT or Mencevax ACWY
SAP version	Version 2
SAP date	12-May-2017
Scope:	All data pertaining to the above study.
Co-ordinating author:	PPD
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LIST OF ABBREVIATIONS

AE	adverse event
ATP	according-to-protocol
BD	blood draw
CI	confidence interval
CSR	clinical study report
ESFU	extended safety follow-up
GBS	Guillain-Barré syndrome
GMC	geometric mean concentration
GMT	geometric mean titer
GSK	GlaxoSmithKline
LL	lower limit
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY-TT	meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine
NOCI	new-onset chronic illness
PHE	Public Health England
rSBA	serum bactericidal assay using rabbit complement
rSBA-MenA	serum bactericidal assay using rabbit complement to measure activity against <i>Neisseria meningitidis</i> group A
rSBA-MenC	serum bactericidal assay using rabbit complement to measure activity against <i>Neisseria meningitidis</i> group C
rSBA-MenW-135	serum bactericidal assay using rabbit complement to measure activity against <i>Neisseria meningitidis</i> group W-135
rSBA-MenY	serum bactericidal assay using rabbit complement to measure activity against <i>Neisseria meningitidis</i> group Y
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TFL	tables, figures, and listings (annexed to SAP)
TT	tetanus toxoid
UL	upper limit

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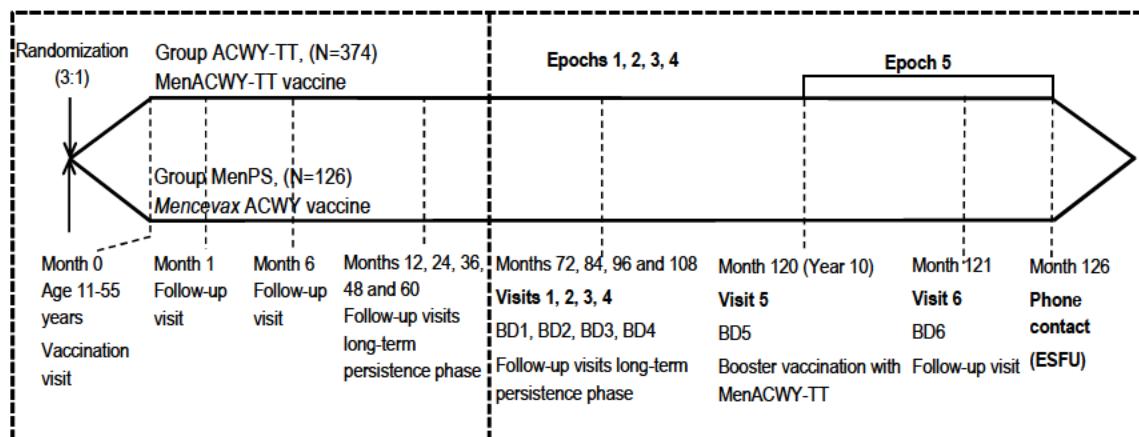
1. DOCUMENT HISTORY

Date	Description	Protocol Version
13-May-2015	Version 1	Final - 07-Nov-2012
12-May-2017	Version 2 SAP amended to reflect sponsorship change to Pfizer following the acquisition of the GSK meningococcal vaccine by Pfizer on 01-Oct-2015	Amendment 1 - 03-Feb-2016

2. INTRODUCTION

The complete statistical analysis plan and results presentation is divided into 2 parts: the first part detailing the analyses to be performed (known as SAP, current document) and a second part, annex (-es) (called TFL) describing the flow and format of tables, figures, and listings to be annexed to the clinical study report (CSR).

3. STUDY DESIGN



MENACWY-TT-015 (107386);
MENACWY-TT-016 EXT:015 Y1 (107392);
MENACWY-TT-017 EXT:015 Y2 (107398);
MENACWY-TT-018 EXT:015 Y3 (107402);
MENACWY-TT-019 EXT:015 Y4 (107404);
MENACWY-TT-020 EXT:015 Y5 (107406)

MENACWY-TT-099 EXT015 Y6,7,8,9,10 (116725)

BD = blood draw

ESFU = extended safety follow-up

TT = tetanus toxoid

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Note: Epoch 001 ie, Visit 1 (Month 72 [Year 6]) was not done (see Section 10: Changes From Planned Analyses).

- Experimental design: Phase IIIb, open, multi-center study with 2 parallel groups.
- Duration of the study:

Persistence phase

- Epoch 001: Persistence Visit 1 (Month 72 [Year 6] after primary vaccination) – Not done due to delay in approval (see Section 10: Changes From Planned Analyses).
- Epoch 002: Persistence Visit 2 (Month 84 [Year 7] after primary vaccination).
- Epoch 003: Persistence Visit 3 (Month 96 [Year 8] after primary vaccination).
- Epoch 004: Persistence Visit 4 (Month 108 [Year 9] after primary vaccination).

Booster phase

- Epoch 005: Booster starting at Visit 5 (Month 120 [Year 10] after primary vaccination) and ending at the phone contact (Month 126 or 6 months after booster vaccination)
- Control: active control for persistence phase (MenPS group), uncontrolled for booster phase (all subjects receive the same booster vaccination).
- Vaccination schedule: At Visit 5 (Month 120 after primary vaccination), 1 dose of meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (MenACWY-TT) will be administered to the subjects in both study groups.
- Blinding: open-label

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	ACWY-TT	Subjects who have received MenACWY-TT in the primary study MenACWY-TT- 015
2	MenPS	Subjects who have received Mencevax ACWY in the primary study MenACWY-TT- 015

The following subgroups, defined based on the age stratum at the time of vaccination in primary study MenACWY-TT-015 in which the subject is enrolled, will be used in analyses of demography, safety, reactogenicity, and immunogenicity.

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Subgroup order in tables	Subgroup label in tables	Subgroup definition for footnote
1	11-17 Years	Subjects aged 11-17 years of age at the time of vaccination in the primary study MenACWY-TT-015
2	18-55 Years	Subjects aged 18-55 years of age at the time of vaccination in the primary study MenACWY-TT-015

4. OBJECTIVES

4.1. Primary Objective

Long-term persistence phase: 6, 7, 8, 9, and 10 years after primary vaccination with MenACWY-TT or Mencevax ACWY, in Study MenACWY-TT-015

- To evaluate the long-term persistence of the serum bactericidal (antibody) titers induced by MenACWY-TT vaccine as compared to Mencevax ACWY when administered to individuals 11-55 years of age in terms of the percentage of subjects with *Neisseria meningitidis* group A (MenA), group C (MenC), group W-135 (MenW-135), and group Y (MenY) titers $\geq 1:8$, $\geq 1:128$, and geometric mean titers (GMTs) as measured by serum bactericidal assay using rabbit complement (rSBA).

Note that since the Year 6 (Month 72) visit was not done (see Section 10: Changes From Planned Analyses) the Year 6 analyses are not applicable.

4.2. Secondary Objectives

One (1) month after booster vaccination with MenACWY-TT vaccine 10 years after primary vaccination:

- To evaluate the immunogenicity of a booster vaccination of MenACWY-TT with respect to the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers $\geq 1:8$, $\geq 1:128$, and GMTs
- To evaluate the immunogenicity of booster vaccination in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY vaccine response*.

*rSBA vaccine responses for groups A, C, W-135, and Y are defined as:

- For initially seronegative subjects (prevaccination titer below the cutoff of 1:8): rSBA antibody titers $\geq 1:32$ 1 month after vaccination, and

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- For initially seropositive subjects (prevaccination titer $\geq 1:8$): rSBA antibody titers at least 4 times the prevaccination antibody titers, 1 month after vaccination

Prebooster and 1 month after booster vaccination with MenACWY-TT vaccine 10 years after primary vaccination:

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

Secondary safety objective:

- To evaluate the safety and reactogenicity of a booster vaccination of MenACWY-TT in terms of solicited events, unsolicited adverse events (AEs), serious adverse events (SAEs) and new-onset chronic illnesses (NOCIs) (eg, autoimmune disorders, asthma, type I diabetes, and allergies).

5. ENDPOINTS

5.1. Primary Endpoint

Immunogenicity with respect to the components of the investigational vaccine 6, 7, 8, 9, and 10 years after primary vaccination in Study MenACWY-TT-015:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers $\geq 1:8$, $\geq 1:128$, and GMTs.

Note that since the Year 6 visit was not done (see Section 10: Changes From Planned Analyses) the primary endpoint with respect to 6 years after primary vaccination is not applicable.

5.2. Secondary Endpoints

Immunogenicity with respect to the components of the investigational vaccine 1 month after booster vaccination at 10 years after primary vaccination:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers $\geq 1:8$, $\geq 1:128$, GMTs, and rSBA vaccine response.

Immunogenicity with respect to the components of the investigational vaccine prebooster and 1 month after booster vaccination at 10 years after primary vaccination:

- Anti-TT concentrations ≥ 0.1 IU/mL, ≥ 1.0 IU/mL, and GMCs.

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Safety and reactogenicity

- Occurrence of solicited local and general events on Days 0-3 following the booster vaccination.
- Occurrence of unsolicited AEs up to 31 days following booster vaccination.
- Occurrence of SAEs, and NOCIs (eg, autoimmune disorders, asthma, type 1 diabetes, and allergies), Guillain-Barré syndrome (GBS) and meningococcal disease from administration of the vaccine dose until study end.

6. STUDY POPULATION

Several cohorts are defined for the purpose of analysis.

6.1. Total Cohort at Year X

This will include all vaccinated subjects in the primary study MenACWY-TT-015 who return for Year X.

Note that since the Year 6 (Month 72) visit was not done (see Section 10: Changes From Planned Analyses) the total cohort at Year 6 is not applicable.

6.2. According-to-protocol (ATP) Cohort for Persistence at Year X

The ATP cohort for antibody persistence at Year X will include all evaluable subjects:

- who were eligible in Study MenACWY-TT-015 (107386).
- who have received the primary vaccination with MenACWY-TT or Mencevax ACWY during Study MenACWY-TT-015 (107386).
- who have available assay results for at least one tested antigen at Year X.
- who have not received a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine not planned in Study MenACWY-TT-015 (107386) before Year X.
- who do not have a history of meningococcal group A, C, W-135, and Y disease prior to Year X.
- who comply with the blood sampling intervals defined in Table 5 of the protocol for Year X.

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- who do not have an immune compromising medical condition.
- who have not received 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 in the primary study MenACWY-TT-015 (107386) and from the previous ATP persistence cohorts, unless the reason for exclusion was either noncompliance with the protocol defined blood sampling windows or a lack of availability of immunogenicity results at a previous time point.

Note that since the Year 6 (Month 72) visit was not done (see Section 10: Changes From Planned Analyses) the ATP cohort for persistence at Year 6 is not applicable.

6.3. Adapted ATP Cohort

When presenting different time points, the adapted ATP cohort will be used to denote that for each time point, the corresponding ATP cohort for immunogenicity/persistence has been used.

More specifically:

- the analyses on the pre and post primary time points will be based on the ATP cohort for immunogenicity defined in MenACWY-TT-015.
- the analyses on Year 1, 2, 3, 4, and 5 time point will be based on the ATP cohort for persistence in MenACWY-TT-016, 017, 018, 019, and 020, respectively.
- the analyses on Year 6, 7, 8, 9, and 10 time points are based on the ATP cohort for persistence at Year 6, 7, 8, 9, and 10 in MenACWY-TT-099, respectively.

Note that since the Year 6 (Month 72) visit was not done (see Section 10: Changes From Planned Analyses) the adapted ATP cohort for persistence at Year 6 is not applicable.

6.4. Total Enrolled Cohort

The total enrolled cohort will include all the subjects who were vaccinated in primary study MenACWY-TT-015 and enrolled in Study MenACWY-TT-099 (C0921002) irrespective of the visit at which they were enrolled.

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6.5. Booster Total Vaccinated Cohort at Year 10

The booster total vaccinated cohort for safety following the booster vaccination at Year 10 will include all vaccinated subjects in the primary vaccination study MenACWY-TT-015 with a booster vaccine administration documented.

For the analysis of immunogenicity after the booster vaccination, the booster total vaccinated cohort at Year 10 will include all subjects for whom data concerning postbooster immunogenicity endpoint measures are available.

6.6. Booster According-to-Protocol (ATP) Cohort For Safety at Year 10

The booster ATP cohort for safety following booster vaccination at Year 10 will include all subjects:

- who met all inclusion criteria and no exclusion criteria for the study
- who have received a dose of study vaccine MenACWY-TT or Mencevax ACWY in the primary study MenACWY-TT-015.
- who have not received a vaccine not specified or forbidden in the protocol (subjects who received a vaccine not foreseen by the study protocol from 30 days before until 30 days after the study vaccine dose will be eliminated from the ATP cohort for safety at Year 10 if the vaccine not foreseen by the protocol was administered before the post-vaccination blood sample).
- who have received a booster dose of study vaccine.
- for whom the administration site of the vaccine is known

6.7. Booster According-to-Protocol (ATP) Cohort for Immunogenicity at Year 10

The booster ATP cohort for immunogenicity at Year 10 will include all evaluable subjects (ie, those meeting all eligibility criteria, complying with the procedures defined in the protocol and with no elimination criteria during the study) from the booster ATP cohort for safety at Year 10 for whom assay results are available for antibodies against at least 1 study vaccine antigen component for the blood sample taken 1 month after vaccination, and who were not administered a vaccine not foreseen by the study protocol, before the post-vaccination blood sample. The interval between Visit 5 and Visit 6 for inclusion in the booster ATP cohort for immunogenicity at Year 10 will be defined as 21 to 48 days (see Table 5 of the protocol).

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7. STATISTICAL METHODS

7.1. Persistence Analyses

7.1.1. Analysis of Demographics/Baseline Characteristics

Demographic characteristics will be tabulated for the total cohort at Year X and the ATP cohorts for persistence at Year X:

- The mean age (in years [with the range and standard deviation]) at Year X, sex, geographic ancestry, and age stratum at vaccination in Study MenACWY-TT-015.
- The distribution of subjects enrolled in the study among the study sites, enrollment at each year, and study withdrawal will be tabulated as a whole and per group for the enrolled cohort.

In addition, the following analyses will also be performed by age stratum:

Demographic characteristics: the mean age (in years [with the range and standard deviation]) at Year X, sex, and geographic ancestry, will be tabulated for the ATP cohorts for persistence at Year X.

7.1.2. Analysis of Persistence

For each Year X: The analysis of antibody persistence will be based on the ATP cohort for antibody persistence at Year X. If, for any vaccine group, the percentage of subjects who come back for the Year X follow-up with serological results excluded from the ATP cohort is higher than 5%, a second analysis based on the total cohort at Year X will be performed to complement the ATP analysis.

Table 1. Laboratories Performing rSBAs by Time Point

Study MenACWY-	Time Point	GSK	PHE
TT-015	Prevaccination	X	
	Month 1	X	
TT-016	Year 1	X	
TT-017	Year 2	X	
TT-018	Year 3	X	
TT-019	Year 4		X
TT-020	Year 5		X
TT-099	Month 84 (Year 7)		X
	Month 96 (Year 8)		X
	Month 108 (Year 9)		X
	Month 120 (Year 10)		X
	Month 121		X

GSK = GlaxoSmithKline; PHE = Public Health England; rSBA = serum bactericidal assay using rabbit complement

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7.1.2.1. Within Group Analysis

For each vaccine group, at each blood sampling time point in Study MenACWY-TT-099, for each antigen assessed:

- GMTs with 95% CIs will be tabulated.
- Percentages of subjects with titers above the proposed cutoffs with exact 95% CIs will be calculated.
- The distribution of antibody titers will be tabulated and also presented using reverse cumulative distribution curves.

In addition, the following analyses will also be performed by age stratum:

- GMTs with 95% CIs will be tabulated.
- Percentages of subjects with titers above the proposed cutoffs with exact 95% CIs will be calculated.
- Geometric mean anti-TT concentrations (GMCs) with 95% CIs will be tabulated.

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7.1.3. Analysis of Safety (Persistence Epoch)

All deaths and SAEs considered related to study procedures reported from the last persistence visit in the previous study to the visit in the current study will be described in detail.

Listings will be compiled for:

All SAEs

Intercurrent medical conditions

AEs/SAEs leading to withdrawal

SAEs related to study vaccination or AEs/SAEs related to lack of vaccine efficacy

SAEs related to study participation/procedures

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7.2. Postbooster Analyses

7.2.1. Analysis of Demographics/Baseline Characteristics

The following analyses will be provided for the booster total vaccinated cohort at Year 10 and the booster ATP cohort for immunogenicity at Year 10.

- Demographic characteristics of each study cohort will be tabulated: the mean age (in years [with the range and standard deviation]) at booster vaccination, sex, geographic ancestry, and age stratum at vaccination in Study MenACWY-TT-015.
- The distribution of subjects enrolled among the study sites will be tabulated as a whole and per group.

In addition the following analyses will also be performed by age stratum:

Demographic characteristics for the booster ATP cohort for immunogenicity at Year 10 will be tabulated: the mean age (in years [with the range and standard deviation]) at booster vaccination, sex, and geographic ancestry.

7.2.2. Analysis of Postbooster Immunogenicity

The analysis of postbooster immunogenicity will be based on the booster ATP cohort for immunogenicity at Year 10. If, for any vaccine group, the percentage of subjects who come back for the Year 10 follow-up with serological results excluded from the booster ATP cohort higher than 5%, a second analysis based on the booster total vaccinated cohort at Year 10 will be performed to complement the ATP analysis.

7.2.2.1. Within Group Analysis

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

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

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In addition the following analyses will also be performed by age stratum:

- GMTs/GMCs with 95% CIs will be tabulated.
- Percentages of subjects with titers/concentrations above proposed cutoffs and vaccine response with 95% CIs will be calculated.
- Percentage of subject seroconverted for anti-TT concentration with 95% CIs will be calculated.

7.2.3. Analysis of Postbooster Safety

The primary analysis will be performed on the booster total vaccinated cohort at Year 10. If more than 5% of the enrolled subjects are eliminated from the booster ATP cohort for safety at Year 10 then a second analysis will be performed on the booster ATP cohort for safety at Year 10 to support the analyses of the booster total vaccinated cohort at Year 10.

For each vaccine group, after the booster vaccination at Visit 5:

The percentage of subjects with at least one local event (solicited events and unsolicited AEs), with at least one general event (solicited events and unsolicited AEs) during the 4-day (Days 0-3) solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for events rated as Grade 3 and for events related to vaccination.

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 0.5°C cumulative increment as well as the percentage of subjects with oral temperature $>39.5^{\circ}\text{C}$.

The verbatim reports of unsolicited AEs will be reviewed by clinicians and the signs and events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with unsolicited AEs within 31 days after vaccination (Days 0-30) and its exact 95% CI will be tabulated by group and by MedDRA preferred term. Similar tabulation 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.

The number and percentage of subjects who experienced SAEs and NOCIs within 6 months following vaccination will be tabulated with exact 95% CI.

The percentage of subjects using concomitant medication (any medication, any antipyretic/analgesic, any antipyretic/analgesic taken prophylactically, respectively) during

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the 4-day and 31-day follow-up periods (Days 0-3 and Days 0-30, respectively) after vaccination will be summarized.

All deaths, SAEs considered related to study procedures or to study vaccination, or cases of GBS or meningococcal disease reported from the booster vaccination visit to the extended safety follow-up (ESFU) phone contact in the current study will be described in detail.

8. STATISTICAL CALCULATIONS

8.1. Derived and Transformed Data

8.1.1. Demography

- Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity. In case of partial dates of any of these 2 dates:
 - 15th of month, if only the day is missing.
 - 30th of June, if day and month are missing.

8.1.2. Immunogenicity

- For a given subject and a given immunogenicity measurement, missing or nonevaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or nonevaluable measurements.
- The cutoff value is defined by the laboratory before the analysis and is described in Section 5.7.3 of the protocol.
- A seronegative subject is a subject whose blood sample titer/concentration is below the cutoff value.
- A seropositive subject is a subject whose blood sample titer/concentration is greater than or equal to the cutoff value.
- The geometric mean titer/concentration (GMT/GMC) calculations are performed by taking the antilog of the mean of the log titer/concentration transformations. Antibody titers/concentrations below the cutoff value of the assay will be given an arbitrary value of half the cutoff value for the purpose of GMT/GMC calculation.
- rSBA vaccine response for groups A, C, W-135, and Y after the vaccine dose is defined as:
 - For initially seronegative subjects (prevaccination titer below the cutoff of 1:8): rSBA antibody titers $\geq 1:32$ 1 month after vaccination, and

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- For initially seropositive subjects (prevaccination titer $\geq 1:8$): rSBA antibody titers at least 4 times the prevaccination antibody titers, 1 month after vaccination.
- Seroconversion for anti-TT antibody is defined as the appearance of antibodies (ie, concentration greater than or equal to the cutoff value) in the serum of subjects seronegative before vaccination.

8.1.3. Safety

- For a given subject and the analysis of solicited events within 4 days after vaccination, missing or nonevaluable measurements will not be replaced. Therefore the analysis of the solicited event based on booster total vaccinated cohort at Year 10 will include only vaccinated subjects for doses with documented safety data (ie, event sheets completed). More specifically the following rules will be used:
 - Subjects who documented the absence of a solicited event after 1 dose will be considered as not having that event after that dose.
 - Subjects who documented the presence of a solicited event and fully or partially recorded daily measurements over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
 - Subjects who documented the presence of a solicited event after 1 dose without having recorded any daily measurements will be assigned to the lowest intensity category at that dose (ie, 37.5°C for fever or Grade 1 for other events).
 - Doses without event sheets documented will be excluded.
- For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the AE or the concomitant medication will be considered as subjects without the AE or the concomitant medication respectively.
- For the analysis, oral/axillary/tympanic temperatures will be coded as follows:

Grade	Temperature
0	$<37.5^{\circ}\text{C}$
1	$\geq 37.5^{\circ}\text{C} - \leq 38.0^{\circ}\text{C}$
2	$>38.0^{\circ}\text{C} - \leq 39.0^{\circ}\text{C}$
3	$>39.0^{\circ}\text{C}$

When measured by the rectal route, the corresponding oral temperature will be derived by subtracting 0.5°C from the temperature recorded. The above intensity grade will be applied to the derived oral temperature.

- For the percentage, the way the percentage of subjects will be derived will depend on the event analyzed (see table below for details). As a result, the N value will differ from one table to another.

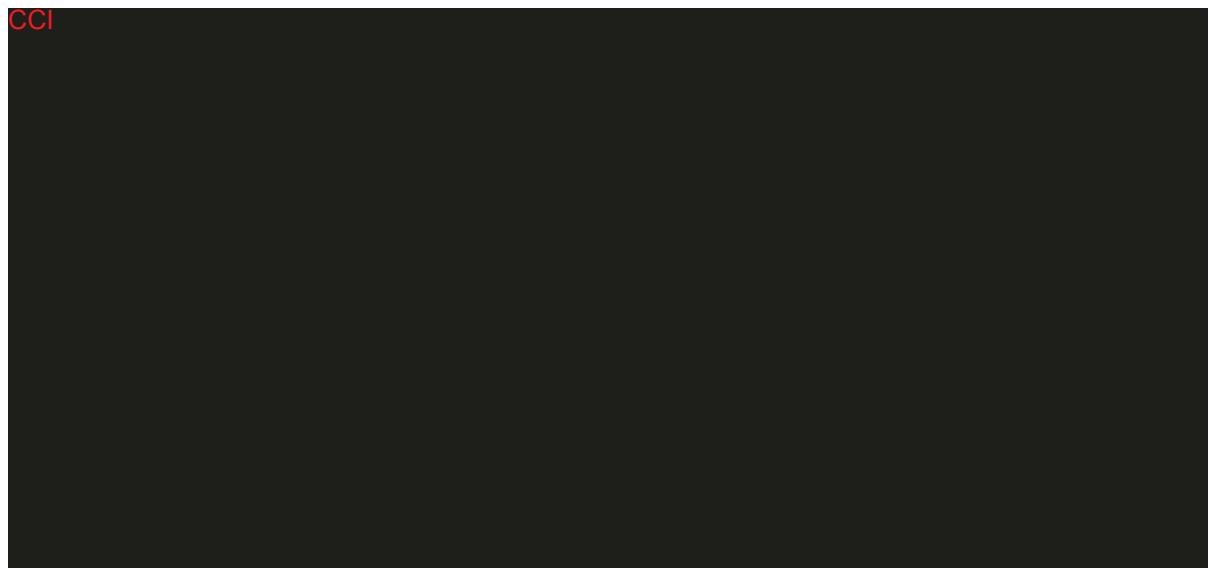
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Event	N used for deriving % per subject for vaccination phase
Concomitant vaccination	All subjects with study vaccine administered
Solicited general event	All subjects with at least one solicited general event documented as either present or absent (ie, event sheets completed)
Solicited local event	All subjects with at least one solicited local event documented as either present or absent (ie, event sheets completed)
Unsolicited AE	All subjects with study vaccine administered
Concomitant medication	All subjects with study vaccine administered

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8.3. Data Presentation Description

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

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
anti-TT	GMC	3
All summaries	% of count, including LL & UL of CI	1

Abbreviations: GMT = geometric mean titer; LL = lower limit; 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; TT = tetanus toxoid; UL = upper limit.

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8.4. Methodology for Computing CI

- All CI computed will be two-sided 95% CI.
- The exact 95% CIs for a proportion within a group will be based on the method by Clopper and Pearson¹.
- The 95% CI for geometric mean titers/concentrations (GMTs/GMCs) will be obtained within each group separately. The 95% CI for the mean of log-transformed titer will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer/concentration.

9. CONDUCT OF ANALYSES

9.1. Sequence of Analyses

The persistence analysis will be done in a stepwise fashion after the persistence time points for Years 7, 8, and 9 as soon as the results are available.

The analysis of persistence at Year 10, and immunogenicity, safety, and reactogenicity for the booster vaccination will be done after the booster time point as soon as the results are available for Visit 5, Visit 6, and the ESFU.

The persistence and safety analyses at the end of the study (Month 126) will be done on clean data. All analyses will be done on a validated and frozen database.

An integrated CSR will include all analyses on persistence as well as booster data.

9.2. Statistical Considerations for Interim Analyses

No statistical adjustment for the sequence of analysis is required since the study is descriptive.

10. CHANGES FROM PLANNED ANALYSES

Please note that the changes from the planned analysis to be included in the CSR will be identified during the CSR review.

- The concept of adapted ATP cohorts, adapted total cohort, and total enrolled cohort are explained in detail in Section 6.

Statistical Analysis Plan



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- Study visit for Year 6 (Month 72) was not done because approval was not obtained from the authorities until after the end of the Visit 6 window. No activity was done for Year 6 (Month 72).
- The name of total vaccinated cohort at Month 121 has been changed to booster total vaccinated cohort at Year 10, name of ATP cohort for safety at Month 121 has been changed to booster ATP cohort for safety at Year 10, and name of ATP cohort for immunogenicity at Month 121 has been changed to booster ATP cohort for immunogenicity at Year 10.

11. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26:404-413.