Statistical Analysis Plan

Study alias & e-track number(s): V59_77 (205352)

Version: 1 Date: 19-09-2016

Detailed Title:	A Phase 3b, Controlled, Open-Label, Multi-Center Study to Evaluate Safety and Immunogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination.
Scope:	All data pertaining to the above study.
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TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
ES	Exposed Set
FAS	Full Analysis Set
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PD	Protocol Deviation
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content

1. DOCUMENT HISTORY

Date	Description	Protocol Version
19-SEP-2016	Version 1: first version	Final Version 1 – 24-JUN-2016

2. STUDY DESIGN

This is a phase 3b, controlled, open-label, multi-center study to evaluate safety and immunogenicity of MenACWY-CRM after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years before and in vaccine-naive individuals.

Study population: Approximately 700 healthy subjects 15 through 55 years of age will be enrolled in the study.

Duration of the study: The duration of this study is approximately 6 months per subject.

Written informed consent and, as applicable according to local guidelines, written assent will be obtained before conducting any study-specific procedures.

Vaccination schedule: All subjects will receive a single dose of MenACWY-CRM at Day 1.

Study groups:

Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menveo 4 to 6 years before, will receive one dose of MenACWY-CRM.

Group Menactra-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menactra 4 to 6 years before, will receive one dose of MenACWY-CRM.

Group Naive: approximately 100 subjects equally enrolled across all clinical sites, who have not received any meningococcal vaccination, will receive one dose of MenACWY-CRM.

Randomization / Stratification:

Within each study group, subjects will be randomized into one of two different blood draw schedules according to a 1:1 ratio, described as follows:

- Subjects getting blood draws at Day 1, Day 4 and Day 29.
- Subjects getting blood draws at Day 1, Day 6 and Day 29.

Table 2-1: Schematic diagram of the V59_77 study groups

Vaccine History	Vaccination in current study	Blood draw schedule
Menveo N=300	Menveo	Blood draw Day 1, 4, 29 (N=150)
		Blood draw Day 1, 6, 29 (N=150)
Menactra N=300	Menveo	Blood draw Day 1, 4, 29 (N=150)
		Blood draw Day 1, 6, 29 (N=150)
Vaccine-Naive N=100	Menveo	Blood draw Day 1, 4, 29 (N=50)
		Blood draw Day 1, 6, 29 (N=50)

Blinding: open-label study.

Blood samples: Three (3) blood samples of approximately 10 mL each will be collected according to the blood draw schedule in Table 2-1.

Data collection: Electronic Case Report Form (eCRF).

Study clinic visits: Three (3) clinic visits at Day 1, Day 4 or Day 6 and Day 29 are planned for each subject.

Reminder Phone calls: Two (2) reminder phone calls will be conducted at Day 3 and Day 5 after the study vaccination to remind the subject/legal guardian to complete the diary card.

Safety phone calls: Three (3) safety phone calls (at Day 15, Day 91 and Day 181) will be conducted to collect any medically-attended AEs, AEs leading to withdrawal, SAEs, related medications and any vaccinations. In addition, all unsolicited AEs and related medications occurring after the vaccination will be collected during the safety call at Day 15. The Day 181 Safety Phone call will also serve as the termination visit.

Solicited Adverse Events (injection site pain, erythema, induration, fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills and fever) occurring on the day of vaccination and the following six days (Day 1 through Day 7) will be recorded daily using a Diary Card for all subjects.

Unsolicited AEs occurring within 28 days after study vaccination will be collected. Qualified site staff will interview the subject by phone approximately 14 days after vaccination and in person at the study site approximately 28 days after study vaccination to assess the occurrence of any unsolicited AEs.

Medically-attended AEs, AEs leading to study withdrawal and SAEs will be collected during the entire study period. These data will be captured by interviewing the subject and/or subjects' parents / guardian (as applicable) during the site visits and phone calls and by review of available medical records. Subjects and/or parents / guardian will be encouraged to call the site in the event of any medically-attended AEs or any AEs which they perceive as being of concern during the entire study period.

Table 2-2: Schematic diagram of the V59_77 study design

Day 1	Day 4 (-1/+1)	Day 6 (-1/+1)	Day 15 (-2/+2)	Day 29 (-7/+14)	Day 91 (-14/+14)	Day 181 (-14/+14)
Blood draw (all subjects) Menveo	Blood draw (50% of subjects)	Blood draw (50% of subjects)	Safety Phone call	Blood draw (all subjects)	Safety Phone call	Safety Phone call Study termination

3. OBJECTIVES

3.1. Primary Objective(s)

Immunogenicity objective:

1. To demonstrate a sufficient immune response following a booster dose of MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menveo, as measured by the percentage of subjects with hSBA seroresponse[1] against *N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccination
2. To demonstrate a sufficient immune response following a booster dose of MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menactra, as measured by the percentage of subjects with hSBA seroresponse[1] against *N. meningitidis* serogroups A, C, W and Y at Day 29 after vaccination

   Criteria to demonstrate immune response sufficiency: The immune response sufficiency will be tested sequentially; first in the group of subjects who received primary vaccination with Menveo and, if met, also in the group of subjects who received primary vaccination with Menactra . The immune response will be considered as sufficient if the lower limit of the one-sided 97.5% CI for percentage of subjects with hSBA seroresponse[1] against serogroups A, C, W and Y is greater than 75%. The study will be considered successful if the immune response sufficiency will be demonstrated at least in the group of subjects who received primary vaccination with Menveo.

3.2. Secondary Objective(s)

Secondary Immunogenicity objectives:

1. To compare the immune responses over time following a booster dose of MenACWY-CRM vaccine, between subjects who previously received Menveo,

[1] Seroresponse is defined for this booster study as follows: For subjects with pre-vaccination titers <4, post-vaccination titers ≥ 16; for subjects with pre-vaccination titers ≥4, post vaccination titers at least 4 times the pre-vaccination titers.

subjects who previously received Menactra, and subjects who previously received Menveo or Menactra (pooled vaccine group) and following a single dose in vaccine-naive individuals, as measured by the percentages of subjects with hSBA seroresponse[1], hSBA titers ≥8 and ≥16, and hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6, and Day 29 after vaccination.

2. To assess persistence of bactericidal antibodies against serogroups A, C, W and Y at approximately 4-6 years after the primary vaccination with Menveo and after the primary vaccination with Menactra in comparison with naturally-acquired level in vaccine-naive individuals, as measured by the percentages of subjects with hSBA titers ≥8 and hSBA GMTs at Day 1.

Secondary Safety objectives:

To assess the reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra and vaccine-naive individuals.

4. ENDPOINTS

4.1. Primary Endpoints

Primary Immunogenicity Endpoint

The following measure will be summarized for the Menveo-Menveo and Menactra-Menveo groups:

1. Percentage of subjects with hSBA seroresponse[2] against *N. meningitidis* serogroups A, C, W and Y at Day 29.

[2] Seroresponse is defined for this booster study as follows: For subjects with pre-vaccination titers <4, post-vaccination titers ≥ 16; for subjects with pre-vaccination titers ≥4, post vaccination titers at least 4 times the pre-vaccination titers.titers.

4.2. Secondary Endpoints

Secondary Safety Endpoints

Safety of the study vaccine will be assessed in the Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups in terms of the frequencies (percentages) of reported adverse events including:

1. Any unsolicited AEs reported within 30 minutes after vaccination;
2. Solicited local and systemic AEs reported from Day 1 (6 hours) through Day 7 after vaccination;
3. Other indicators of reactogenicity (e.g. use of analgesics / antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEs reported from Day 1 through Day 29 after vaccination;
5. Medically-attended AEs, AEs leading to withdrawal and SAEs reported from Day 1 through Day 181 (entire study period).

Adverse events will be coded using MedDRA preferred terms as applicable.

Secondary Immunogenicity Endpoints

The following measures will be summarized for Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups:

1. Percentage of subjects with hSBA titer ≥8 and ≥16 against *N. meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6 and Day 29 and between-group differences;
2. Percentages of subjects with hSBA seroresponse[3] against *N. meningitidis* serogroups A, C, W and Y at Day 4, Day 6 and Day 29 and between-group differences;

[3] Seroresponse is defined for this booster study as follows: For subjects with pre-vaccination titers <4, post-vaccination titers ≥ 16; for subjects with pre-vaccination titers ≥4, post vaccination titers at least 4 times the pre-vaccination titers.

3. hSBA GMTs against *N. meningitidis* serogroup A, C, W and Y at Day 1, Day 4, Day 6 and Day 29;
4. Ratios of hSBA GMTs at Day 1, Day 4, Day 6 and Day 29 (between study groups).
5. hSBA Geometric Mean Ratios (GMRs) at Day 4, Day 6, and Day 29 compared to Day 1 (within study groups).

5. ANALYSIS SETS

5.1. Definition

5.1.1. All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a Subject ID.

5.1.2. All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

5.1.3. Safety Sets

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

5.1.4. Immunogenicity Sets

Full Analysis Set (FAS)

FAS (Day 1)

All subjects in the All Enrolled Set who:

- are randomized;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup.

FAS (Day 29)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide evaluable serum samples at Day 1 whose result is available for at least one serogroup (this condition is not required for the analyses on hSBA titer ≥8 and ≥16, GMTs and GMRs calculated at specific timepoints);
- provide evaluable serum samples at Day 29 whose result is available for at least one serogroup.

Per Protocol (PP) Set

A PPS will be defined for each FAS described in the previous Section with additional criteria specified below.

All subjects in the FAS Immunogenicity who:

- Have no protocol deviations leading to exclusion (see section 5.2.3) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to the analysis (see section 5.2.3)

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each sets. A consolidated table is also available in Annex 2.

5.2.1. Elimination from Exposed Set (ES)

Code 100 (Study vaccine not administered at all) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Full Analysis Set (FAS)

Code 110.x (Serological results not available at Day x) will be used for identifying subjects eliminated from FAS Day x.

5.2.3. Elimination from Per-protocol analysis Set (PPS)

5.2.3.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions:

Code	Condition under which the code is used
120	Randomization failure
140	Vaccination not according to protocol
150	Administration of forbidden vaccine
200	Subject did not meet entry criteria
230	Administration of forbidden medication
240	Underlying medical condition forbidden by the protocol
250	Concomitant infection related to the vaccine which may influence immune response

260	Did not comply with study vaccination schedule

5.2.4. Right censored Data

Not applicable.

5.2.5. Visit-specific censored Data

Data from visit x will be censored for the PPS analysis under the following conditions.

Code	Condition under which the code is used
112.x	Obvious deviation from Laboratory Manual or error in laboratory data at Day x
270.x	Did not comply with blood draw schedule at Day x

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

Not applicable.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in annex 1 and will not be repeated below.

6.1. Demography

6.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated overall and by study group.

Distributions of subjects by sex, race and ethnic origin will be summarized overall and by study group.

6.1.2. Additional considerations

The frequencies and percentages of subjects with medical history will be presented by MedDRA system organ class and preferred term, by study group and overall.

Medical history and demographic data will be tabulated for the All Enrolled, PPS (Day 29) and Overall Safety set.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

Subjects will be analyzed to the extent that they were exposed to study vaccines and according to the available safety data for the subject during any study period. Subjects who withdraw early or who are lost to follow-up will be removed from the summary table denominator for the time period in which they have no available safety data collected.

6.2.2. Additional considerations

The frequencies and percentages of subjects with vaccination will be summarized overall and by study group. Data will be tabulated for the All Enrolled Set.

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

The analysis population to be used for the primary objectives is the PPS (Day 29). Analyses of primary objectives will be repeated on the FAS (Day 29) to assess robustness of results. Analyses of secondary immunogenicity will be based on the PPS and repeated on the FAS.

Missing immunogenicity values are assumed MCAR (Missing Completely At Random) and therefore may not contain information that impact the result of the analysis (i.e., not informative). Imputation methods will therefore not be used.

The hSBA titers at each visit will be logarithmically transformed (base10) to obtain approximately normally distributed data.

For comparison of percentages and GMT ratios, unadjusted estimates will be obtained along with adjusted estimates from regression models to account for potential baseline imbalance between study groups. For each *N. meningitidis* serogroup A, C, W and Y, unadjusted GMTs will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. Adjusted GMTs will be obtained from Analysis of Covariance (ANCOVA) models.

Seroresponse (Day 4, Day 6, and Day 29)

The percentage of subjects with seroresponse and associated two-sided 95% Clopper-Pearson CIs will be computed by group (Menveo-Menveo, Menactra-Menveo, the Naïve and the pooled [Menveo-Menveo and Menactra-Menveo] groups) and *N. meningitidis* serogroups A, C, W and Y test strains. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen & Nurminen score method.

In a descriptive fashion - using the difference in percentages and 95% CIs - each of the previously vaccinated groups (individually and pooled [Menveo-Menveo and Menactra-Menveo]) will be compared to the naïve group. Also the two previously vaccinated study groups will be compared to each other.

As sensitivity analyses, the difference in percentages will also be obtained from a log-linear model adjusting for pre-vaccination titer.

Percentage of Subjects With hSBA titer≥8 and ≥16 (Day 1, Day 4, Day 6, and Day 29)

For each study group and in the pooled group (Menveo-Menveo and Menactra-Menveo), the percentage of subjects with hSBA titer ≥8 and ≥16 and associated two-sided 95% Clopper-Pearson CIs will be computed by the *N. meningitidis* serogroups A, C, W and Y test strains on Day 1, Day 4, Day 6 and Day 29 (as applicable, depending on blood draw schedule).

Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen & Nurminen score method.

In a descriptive fashion - using the difference in percentages and 95% CIs - the previously vaccinated groups (individually and pooled [Menveo-Menveo and Menactra-Menveo]) will be compared to the naïve group. Also the two previously vaccinated groups will be compared to each other.

As sensitivity analyses, the difference in percentages will also be obtained from a log-linear model adjusting for pre-vaccination titer.

Between-group Ratios of GMTs (Adjusted and Unadjusted)

The between-group ratio of hSBA GMTs and corresponding 95% CI, at each of Visit Day 1 (Persistence), Day 4, Day 6 and Day 29 against each *N. meningitidis* serogroups A, C, W and Y test strains will be obtained by exponentiating the mean between-group differences in log-transformed titers and the corresponding 95% CIs at each of the timepoints specified.

Additionally, adjusted ratio of GMTs will be obtained from ANCOVA models including pre-vaccination titer as factors in the model.

The previously vaccinated groups (individually and pooled [Menveo-Menveo and Menactra-Menveo]) will be compared to the naïve group at each timepoint – descriptively – using the ratios of GMTs.

The two previously vaccinated groups will be compared at each timepoint using GMT ratios.

Within-group GMRs (Adjusted and Unadjusted)

Within each study group and for each serogroup, GMRs will be calculated, as applicable, at:

- Visit Day 4 versus at Visit Day 1;
- Visit Day 6 versus at Visit Day 1; and
- Visit Day 29 versus at Visit Day 1.

The unadjusted GMRs and 95% CIs will be constructed by exponentiating the mean within-group differences in log-transformed titers and the corresponding 95% CIs.

6.3.2. Additional considerations

Using the PPS (Day 29), the analyses of the primary objectives will be replicated by sex and race.

All sensitivity analyses will be performed on the PPS.

Reverse Cumulative Distributions Curves of hSBA Titers against *N. Meningitidis* serogroups A, C, W and Y will be produced at Days 1, 4, 6 and 29 for all study groups (Menveo-Menveo, Menactra-Menveo and the Naïve) on both the PPS and the FAS.

The adjusted ratio of GMTs, obtained from ANCOVA models including pre-vaccination titer as factors in the model, will be only computed as secondary analyses. The group titers of naïve subjects will be anyway always summarized without any adjustment (i.e. unadjusted GMTs and percentages).

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

Analyses of solicited adverse events - and other solicited reactions - and unsolicited adverse events will be performed on the relevant safety sets.

For unsolicited adverse events, the entire study period will be divided into the following intervals: onset within 30 minutes after vaccination, onset within 28 days after vaccination; and from Day 1 through Day 181. For solicited adverse events, the solicited study period will be divided into intervals: from 6 hours through day 3; from day 4 through day 7; and from 6 hours through day 7.

No imputation methods will be used to address missing safety data.

Summaries of safety will be presented using frequencies and percentages within each study group. No statistical comparisons among the study groups with respect to any of the safety parameters will be performed.

Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarized for the intervals Day 1 (6 hours) – Day 3, Days 4-7, Day 1 (6 hours) – Day 7 by maximal severity and by study group. Separate analyses will be performed for solicited AEs reported 30 minutes after vaccination. The severity of solicited local adverse events, including injection-site erythema and induration, will be categorized based on linear measurement: None (0-24 mm), Mild (25-50 mm), Moderate (51-100 mm), Severe (> 100mm).

Injection site pain and systemic reactions, including fatigue, headache, myalgia, arthralgia, chills, nausea, loss of appetite, occurring up to 7 days after each vaccination will be summarized according to "mild", "moderate" or "severe".

Each solicited local and systemic adverse event will also be further summarized as "none" versus "any".

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

Body temperature will be summarized separately according to the 3 schemes described below and will be broken down according to route of measurement:

- by 0.5 °C increments from 36.0°C up to ≥40°C;
- by 1°C increments: <36.0, 36.0-36.9, 37.0-37.9, 38.0-38.9, 39.0-39.9, ≥40°C;
- According to different cut-offs (< versus ≥): 38.0, 38.5, 39.0, 39.5, 40.0°C.

Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC).

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to SOC and preferred term within SOC. These summaries will be presented by study group and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine will be counted.

Separate summaries will be produced for the following categories:

- Adverse events that are possibly or probably related to vaccine
- Unsolicited AEs reported within 30 minutes after vaccination
- Unsolicited AEs reported within 29 days after vaccination
- Adverse events leading to withdrawal
- Adverse events leading to a medically attended visit
- Serious adverse events

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

6.4.2. Additional considerations

6.4.2.1. Exclusion of implausible solicited Adverse Event

Some local and systemic adverse events will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible.

Therefore these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the table below:

Table 6.5.2.1-1: Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema	For subjects ≥ 6 years: ≥ 900 mm Measurements < 0 mm
Induration	For subjects ≥ 6 years: ≥ 500 mm Measurements < 0 mm

6.4.2.2. Solicited Adverse Events

For details please refer to section 7.1.1 of the protocol.

Fever, defined as a body temperature of ≥38°C irrespective of route of measurement, will be integrated to the summaries as a systemic adverse event.

The analyses will encompass summaries of the data on five levels:

1. Daily reports of subjects with solicited adverse events.
2. Time of first onset of solicited adverse events (excluding 30 min measurement).
3. Solicited adverse events, maximum event severity by event and interval [6h - day 3, day 4 -7, and 6h - day 7, each without 30 min].
4. Duration of solicited adverse events, including ongoing AE after Day 7.
5. Solicited adverse events and indicators of solicited adverse events, occurrence of at least one event by category (local, systemic) and interval 6h-Day 3, Day 4-7 and 6h-Day 7, each without 30 min].

For each of the time points or time intervals presented in the summaries, only subjects with at least one plausible observation (i.e., any non-missing values but excluding "Not done/unknown" and implausible values) for the solicited adverse events in the interval of interest will be considered. Subjects without plausible data (i.e. missing values or reported as "Not done/unknown" and implausible values) will be removed from the denominator to prevent a downward bias (towards zero).

Level 1: Daily reports of solicited adverse event

For each of the time points (30 min, 6h, days 2, 3, 4, 5, 6 and 7) only subjects with at least one plausible observation (i.e., any non-missing values but excluding "Not done/unknown" and implausible values) for the solicited adverse event in the interval of interest will be considered. Subjects without plausible data (i.e. missing values or reported as "Not done/unknown" and implausible values) will be removed from the denominator in order to prevent a downward bias (towards zero). Data collected will be summarized (frequencies and percentages of subjects) by study group, solicited adverse event and time point.

Level 2: Time of first onset of solicited adverse events

The **time of first onset** is defined, for each subject, for each solicited adverse event, as the time point at which the respective solicited adverse event first occurred. For erythema, and induration the following threshold will be used: $\geq$ 25 mm. The summary will provide the frequencies and percentages of subjects with first onset of each solicited adverse events by study group and by each time point (30 min, 6h, days 2, 3, 4, 5, 6 and 7). Note, 'not done' is treated identical to 'missing'.

Level 3: Solicited adverse events, maximum event severity by event and interval

The **maximum event severity** will be defined if there is at least one plausible non-missing observation (excluding "Not done/unknown" and implausible values) within this time interval. Each subject's data will be aggregated across the time points of the interval and summarized according to the maximal severity observed for each adverse event, followed by a summary across subjects for each vaccine. Subjects without any solicited adverse events in the interval, i.e., missing values at each of the requested time points, will be removed from the denominator.

Level 4: Number of days with solicited adverse events

The number of days with the adverse event is defined irrespective of severity. This means at least 'mild' solicited adverse event that are assessed qualitatively and $\geq$ 25 mm for erythema and induration. If a solicited adverse event continues beyond day 7 the period after day 7 is added.

The frequency distribution of the number of days will be provided in a summary table by vaccine and by adverse event.

Level 5: Solicited adverse events, occurrence of at least one event by category (local, systemic) and interval.

The **occurrence of at least one solicited adverse event** is defined as "any" for a subject if he/she reports greater than "none" ($\geq$ 25 mm, for erythema and induration) for the respective event and "none" otherwise. The occurrence of at least one solicited adverse event (i.e., none versus any) will be summarized by category (i.e., local, systemic, any), by study group and by time interval.

Medications to treat or prevent pain or fever will be summarized by frequencies and percentages of subjects reporting use of the medications by interval (30min, 6h - day 3, day 4 - 7, 6h - day 7).

Safety completeness analysis

The safety completeness analysis on solicited adverse events aims to identify subjects who completed diary cards, irrespective of severity. The analysis will show the number of subjects with *valid data* by solicited adverse event and time point. *Valid data* in the context of the safety completeness analysis are all data entered in the diary card (including implausible values) except "Not done/unknown".

Four summaries will be produced:

1. The frequencies of subjects who provide diary cards by study group.
2. For each solicited adverse event, the frequencies of subjects with *valid data* will be presented by study group and timepoint: 30 min, 6h, days 2, 3, 4, 5, 6 and 7.
3. For each type of solicited adverse event (local, systemic) and indicators of solicited adverse events, such as analgesic use the frequencies of subjects *with valid data* by study group, aggregated over time points: 6h - day 7.
4. For each solicited adverse event, the frequencies of subjects *with valid data* by study group, aggregated over time points: 6h - day 7.

For the corresponding percentages, the denominator will be the respective numbers of exposed subjects, i.e., subjects who received a vaccination and were still in-study for that time point or time interval, irrespective of whether a diary card was present or not.

6.4.2.3. Unsolicited Adverse Events

All AEs occurring during the first 28 days after vaccination, including the day of vaccination, and all medically attended unsolicited adverse events, adverse events leading to study withdrawal and serious adverse events occurring at any time during the study will be recorded according to the protocol-specified reporting rules.

Only vaccine-emergent adverse events (see section 11.2 for definition) will be analyzed, i.e., excluding those after a subject has given informed consent but before vaccination. The selection of unsolicited adverse events and the assignment to time intervals will be done by day of onset and not by days ongoing/persisting.

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited adverse event.
- Possibly or probably related unsolicited adverse events.
- Unsolicited adverse events leading to death.
- Serious adverse events.
- Possibly or probably related serious adverse event.
- Unsolicited adverse events leading to premature withdrawal from study.
- Unsolicited adverse events leading to hospitalization.
- Medically attended adverse events.

Solicited adverse events continuing beyond day 7 will be coded by MedDRA and combined with the respective unsolicited adverse events.

6.4.2.4. Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA as per the following codes:

Solicited symptom	Lower level code	Lower level term
Pain	10022086	Injection site pain
Fever	10016558	Fever
Loss of appetite	10003028	Appetite lost
Erythema	10022061	Injection site erythema
Induration	10022075	Injection site induration
Fatigue	10016256	Fatigue
Headache	10019211	Headache
Myalgia	10028411	Myalgia
Arthralgia	10003239	Arthralgia
Nausea	10028813	Nausea
Chills	10008531	Chills

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and according to occurrence of each event.

6.4.2.5. Clinical Safety Laboratory Investigations

Not applicable.

6.4.2.6. Concomitant Medication

The frequencies and percentages of subjects reporting concomitant medications will be tabulated overall and by study group. Medications (generic drug name) will be coded using the WHODRUG dictionary (see section 11.2 for definition).

7. ANALYSIS INTERPRETATION

Except for analysis on primary immunogenicity objective with predefined success criterion, comparative analyses are descriptive with the aim to characterize the difference between groups. The use of these descriptive analyses should be limited to supportive analysis of confirmatory analyses or hypothesis generation. There are no success criteria associated with the secondary immunogenicity objectives in this study.

With respect to confirmatory analyses the interpretation must be done in a hierarchical manner. To demonstrate immune response sufficiency after MenACWY-CRM booster vaccine administration, the lower limit of the one-sided 97.5% Confidence Interval (CI) for percentage of subjects with hSBA booster seroresponse against each of serogroups A, C, W and Y must be greater than 75%. This will be tested sequentially first in the group of subjects who received primary vaccination with Menveo and, if met, also in the group of subjects who received primary vaccination with Menactra.

Null hypothesis: $P_{ij} \leq 0.75$

versus

Alternative hypothesis: $P_{ij} > 0.75$

Where: P_{ij} is the population booster seroresponse rate; j = 1,2 refer to group Menveo-Menveo (first test) and Menactra-Menveo (second test) respectively; i = 1,2,3,4 refer to serogroup A, C, W and Y respectively. Overall significance level for all hypothesis tests is one-sided $\alpha = 2.5\%$.

Note that the lower limit of the 1-sided 97.5% CI corresponds to the lower limit of the 2-sided 95% CI that will be presented in the statistical output.

The study will be considered successful if the immune response sufficiency will be demonstrated at least in the group of subjects who received primary vaccination with Menveo.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose (CTRS=web posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TF
Final analysis	E1_01	SR and CTRS	Y	Yes	All tables from TF 25-JUL-2016

8.2. Statistical considerations for interim analyses

No interim analysis of data from this study is planned.

9. CHANGES FROM PLANNED ANALYSES

None

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS…)

The mock tables referred under column named 'layout' can be found in the legacy-NV SDD dedicated folder for standard tables.

The following group names will be used in the TFLs:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables	Pooled definition for footnote
1	Menveo-Menveo	Subjects previously vaccinated with Menveo	Pooled Menveo/Menactra - Menveo	Subjects previously vaccinated with Menveo/Menactra
2	Menactra-Menveo	Subjects previously vaccinated with Menactra	Pooled Menveo/Menactra - Menveo	Subjects previously vaccinated with Menveo/Menactra
3	Naive	Naive subjects	Naive	Naive subjects

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STAT METHODS

11.1. Statistical method references

Nauta J. Statistics in Clinical Vaccine Trials. 2010. Heidelberg: Springer.

U.S. Department of Health and Human Services, Food and Drug Administration, CBER (2007): Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413.Miettinen O., Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4(2):213-226.

11.2. Standard data derivation

Immunogenicity

Values below the limit of quantification (recorded as "< LQ") will be set to half that limit.

Seroresponse is defined for this booster study as follows:

- for subjects with pre-vaccination titers <4, post-vaccination titers ≥ 16;
- for subjects with pre-vaccination titers ≥4, post vaccination titers at least 4 times the pre-vaccination titers.

Duration in the Study

Duration in the study is defined in days as:

Last visit date (visit x)[a] – Enrollment date (visit 1) + 1

[a]or premature discontinuation date (in case of withdrawal from the study)

The duration is missing if one of the dates is missing or incomplete.

Unsolicited Adverse Events

All adverse events will be characterized according to the date of occurrence related to the vaccination phase as follows:

- **Emergence before vaccination phase**: start date before the first date of injection of study vaccine.
- **Emergence during vaccination phase**: start date on or after the first date of injection of study vaccine or, adverse event increase in severity including to "serious" adverse event.

If start date is equal to the first date of injection then "timing" variable ("On injection day, before injection"/"On injection day, after injection") will be used to define whether the adverse event occur before or after the injection.

If an adverse event start date is missing or unknown, the adverse event will be considered as emergent.

When start and/or end dates of an adverse event are only partially known, adverse events will be categorized as emergent before, during, or after vaccination phase using the following rules:

- If the partial end date is before (<) the first study vaccination (i.e., year or year & month is/are before the first study vaccination year or year & month) then the adverse event is emergent before vaccination phase.
- If the partial start date is equal or after (≥) the first study vaccination (i.e., year or year & month is/are after or the same as the first study injection year or year & month) then the adverse event is emergent during vaccination phase.

The **maximum event severity** is the greatest severity associated with a preferred term for a reported adverse event according to the following order: Mild < Moderate < Severe. Unknown/ Missing severity is considered as severe (except for the definition of emergence).

Multiple AEs with the same PT for the same subject are counted only once.

Vaccination-related Adverse Events are those for which the cause has been evaluated by the investigator, and recorded either as possibly related, probably related or unknown/ missing.

Prestudy, Concomitant and Post-Vaccination Medications

A previous medication is a medication used only before the first study vaccination (i.e. medication end date < first study vaccination date).

A post-vaccination medication is a medication used only after study vaccination + 28 days (i.e. medication start date > last study vaccination date + 28 days).

All other medications are **concomitant**.

When start and/or end dates of a medication intake are missing, the medication is considered as concomitant with the study vaccination schedule.

If the first study vaccination date is missing then the medication is considered as concomitant with the study vaccination schedule, provided that the study vaccine was administered to the subject.

The business rule can be consulting by clicking on the following icon:

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Table 12-1 Safety Sets

PD code	PD Description	Study Period	*All Exposed Set*	*Safety Set, Unsolicited AEs*	*Safety Set, Solicited AEs*
	Exclusion code		*EXPFL*	*SSUFL*	*SSSFL*
100	Study vaccine not administered AT ALL	D1-D181	*EXC*	*EXC*	*EXC*
115	Subject did not provide any post-vaccination unsolicited safety data	D1-D181	*None*	*EXC*	*None*
116	Subject did not provide any post-vaccination solicited safety data	D1	*None*	*None*	*EXC*

EXC = excluded from this analysis set.

Table 12-2 Immunogenicity Sets

PD code	PD Description	Study Period	*FAS Day 1*	*FAS Day 29*	*PPS Day 1*	*PPS Day 29*
	Exclusion code		***FAS01FL***	***FAS29FL***	***PPS01FL***	***PPS29FL***
100	**Study vaccine not administered AT ALL**	**D1-D181**	*EXC*	*EXC*	*EXC*	*EXC*
110.1	**Serological results are not available at Day 1 for none of the serogroups**	**D1**	*EXC*	*EXC (for seroresponse only)*	*EXC*	*EXC (for seroresponse only)*
110.2	**Serological results are not available at Day 29 for none of the serogroups**	**D29**	*None*	*EXC*	*None*	*EXC*
112.1	**Obvious deviation from Laboratory Manual or error in laboratory data at D1**	**D1**	*None*	*None*	*EXC*	*EXC (for seroresponse only)*
112.2	**Obvious deviation from Laboratory Manual or error in laboratory data at D29**	**D29**	*None*	*None*	*None*	*EXC*
120	**Randomization failure**	**D1- D29**	*None*	*None*	*None*	*EXC (for analysis at D4 and D6 only)*

PD code	PD Description	Study Period	*FAS Day 1*	*FAS Day 29*	*PPS Day 1*	*PPS Day 29*
	Exclusion code		*FAS01FL*	*FAS29FL*	*PPS01FL*	*PPS29FL*
140	Vaccination not according to protocol	D1	*None*	*None*	*None*	*EXC*
150	Administration of forbidden vaccine	D1- D29	*None*	*None*	*None*	*EXC*
200	Subject did not meet entry criteria	D1- D29	*None*	*None*	*EXC*	*EXC*
230	Administration of forbidden medication	D1- D29	*None*	*None*	*None*	*EXC*
240	Underlying medical condition forbidden by the protocol	D1- D29	*None*	*None*	*EXC*	*EXC*
250	Concomitant infection related to the vaccine which may influence immune response	D1- D29	*None*	*None*	*None*	*EXC*
260	Did not comply with study vaccination schedule	D1	*None*	*None*	*None*	*EXC*
270.1	Did not comply with blood draw schedule at Day 1	D1	*None*	*None*	*EXC*	*None*

PD code	PD Description	Study Period	*FAS Day 1*	*FAS Day 29*	*PPS Day 1*	*PPS Day 29*
	Exclusion code		***FAS01FL***	***FAS29FL***	***PPS01FL***	***PPS29FL***
270.2	**Did not comply with blood draw schedule at Day 4 or Day 6**	**D4/D6**	*None*	*None*	*None*	*EXC (for analysis at D4 and D6 only)*
270.3	**Did not comply with blood draw schedule at Day 29**	**D29**	*None*	*None*	*None*	*EXC*

FAS = Full Analysis Set; PPS=Per Protocol Set; EXC = excluded from this analysis set.

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

Not applicable