GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase 2b, randomized, controlled, observer-blind, multi-center, non-inferiority immunogenicity and safety study of two formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) administered to healthy adults 18 to 40 years of age.
eTrack study number and Abbreviated Title	205343 (MENACWY CONJ-032 [V59_71])
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 29-Aug-2018 Amendment 1 Final: 05-Jul-2019
Co-ordinating author:	PPD (Biostatistician)
Reviewed by:	PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Clinical and Epidemiology Research and Development Project Lead) PPD (Clinical Research and Development Lead) PPD (Scientific writer) PPD (Regulatory Affairs representative) PPD (Clinical Safety representative) PPD (Public disclosure representative)
Approved by:	PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Clinical and Epidemiology Research and Development Project Lead) PPD (Clinical Research and Development Lead) PPD (Scientific writer)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BSP	BioStatistics and Statistical Programming
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EoS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
FS	Free Saccharides
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
GSKDRUG	GlaxoSmithKline Drug Dictionary
hSBA	Human Serum Bactericidal Assay
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantitation
LOD	Lower Limit of Detection
MedDRA	Medical Dictionary for Regulatory Activities
N. meningitidis	*Neisseria meningitidis*
PCD	Primary Completion Date

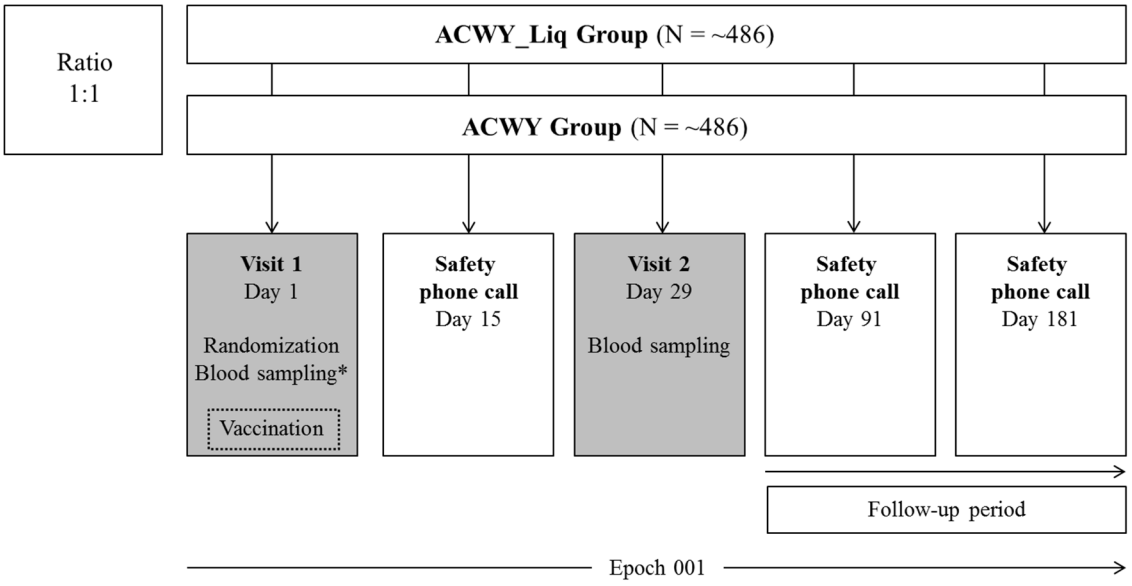
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
YoA	Years of Age

1. DOCUMENT HISTORY

Date	Description	Protocol Version
29-AUG-2018	First version	Protocol Amendment 2: 15-MAR-2018
05-JUL-2019	Amendment 1 Final: List of changes: • Addition of solicited safety sets at 30 minutes and >= 6hours post-vaccination (5.1.3.1) • Addition of permutation test for a sensitivity analysis on the primary objective (6.4.2) • Change of 'probably or possibly related' to 'related' unsolicited AEs to align with the eCRF (6.5) • Sequence of analysis update (8.1) • Changes from planned analyses (9)	Protocol Amendment 3: 08-FEB-2019

2. STUDY DESIGN

Figure 1 Study design overview



* At Visit 1, blood samples will be taken pre-vaccination

- Experimental design: Phase IIB, observer-blind, randomized, controlled, multi-centric study with two parallel groups.
- Duration of the study: for each subject enrolled, the duration will be approximately 6 months.
  - Epoch 001: starting at Visit 1 (Day 1) and ending at last Safety contact (Day 181).
- Primary completion Date (PCD): Visit 2 (Day 29).
- End of Study (EoS): Last subject last visit(LSLV) (Phone call 3 - Day 181) or last testing results released of samples collected at Visit 2 (Day 29)* if it occurs after LSLV.

  *In this case EoS must be achieved no later than 8 months after LSLV.
- Study groups:
  - **Group ACWY_Liq**: ~486 healthy adults receiving a single dose of investigational liquid MenACWY (GSK3536820A) with approximately 30% Men A FS.
  - **Group ACWY**: ~486 healthy adults receiving a single dose of currently licensed GSK' MenACWY vaccine (Menveo).

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
ACWY_Liq	~486	18 – 40 years	x
ACWY	~486	18 – 40 years	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/product name	Study Groups	
		ACWY_Liq	ACWY
MenACWY liquid with approximately 30% MenA FS	MenACWY liquid	x	
Licensed MenACWY (*Menveo**)	MenA lyo		x
	MenCWY liquid		

* *Menveo* commercial formulation consisting of a MenA lyophilized component and a MenCWY liquid component to be reconstituted together before administration (0.5mL).

- Control: active control
- Vaccination schedule: All subjects will receive a single dose of one of the study vaccines at Visit 1 (Day 1).
- Treatment allocation: Subjects will be randomized using a centralized randomization system on internet (SBIR) at Visit 1 (Day 1).
- Blinding: observer-blind.

- Sampling schedule: Blood samples of approximately 20 mL will be taken at Visit 1 (Day 1; pre-vaccination) and Visit 2 (Day 29).
- Type of study: self-contained.
- Data collection: Standardised Electronic Case Report Form (eCRF). Solicited adverse events (AEs) assessed on site during the 30 minutes post-vaccination assessment are to be recorded on the source documents and entered in the eCRF. Solicited AEs occurring after the 30 minutes post-vaccination assessment will be collected only using a subject Diary (electronic Diary [eDiary]).

Table 3 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Visit 1 → Phone call 1	14 days	11 - 17 days
Visit 1 → Visit 2	28 days	21 - 42 days
Visit 1 → Phone call 2	90 days	76 - 104 days
Visit 1 → Phone call 3	180 days	166 - 194 days

3. OBJECTIVES

3.1. Primary objective

- To demonstrate non-inferiority of the investigational liquid MenACWY vaccine with approximately 30% Men A FS to that of currently licensed MenACWY vaccine, as measured by the human serum bactericidal assay (hSBA) Geometric Mean Titers (GMTs) directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  Criterion to demonstrate non-inferiority:

  Non-inferiority will be concluded if the lower limit of the two-sided 95% confidence interval (CI) for the ratio of hSBA GMTs against serogroup A between the liquid formulation and the licensed formulation is greater than 0.5.

3.2. Secondary objectives

- To compare the immunogenicity of the investigational liquid MenACWY vaccine with approximately 30% Men A FS and the currently licensed MenACWY vaccine, as measured by hSBA GMTs directed against *N. meningitidis* serogroups C, W and Y at Day 29.
- To compare the immunogenicity of the investigational liquid MenACWY vaccine with approximately 30% Men A FS to the currently licensed MenACWY vaccine, as measured by the percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1.

  Note: The following definition will be used for 4-fold rise: a) for individuals whose pre-vaccination titers are < the limit of detection (LOD), the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the lower limit of quantitation (LLOQ) whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post vaccination titers must be at least four times the pre-vaccination titer.
- To compare the immunogenicity of the investigational liquid MenACWY vaccine with approximately 30% Men A FS to the currently licensed MenACWY vaccine, as measured by the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 29.

  *Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.
- To assess the safety/reactogenicity of the investigational liquid MenACWY vaccines with approximately 30% Men A FS and the currently licensed MenACWY vaccine.

4. ENDPOINTS

4.1. Primary endpoint

The following measures will be summarized:

- hSBA GMTs against N. meningitidis serogroup A at Day 29, for each vaccine group and between-group ratios.

4.2. Secondary endpoints

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroups A (except Day 29), C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group ratios.
- Within-group ratios of hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1.
- Percentages of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group and between-group differences.

  Note: A 4-fold rise is defined as: a) for individuals whose pre-vaccination titers are < the LOD, the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the LLOQ whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post-vaccination titers must be at least four times the pre-vaccination titer.
- Percentages of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group differences.

  *Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

Safety of the study vaccine formulations will be evaluated for all vaccine groups in terms of the frequency (percentage) of reported adverse events including:

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

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 Set

5.1.3.1. Solicited Safety Set (solicited local and systematic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data. Two solicited safety sets are defined.

5.1.3.1.1. Solicited Safety Set (30 mins)

All subjects in the Exposed Set with any solicited adverse event data within 30 mins after vaccination.

5.1.3.1.2. Solicited Safety Set (6 hours- Day 7)

All subjects in the Exposed Set with any solicited adverse event data 6 hours – Day 7 after vaccination.

5.1.3.2. Unsolicited Safety Set (unsolicited adverse events)

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

5.1.3.3. Overall Safety Set

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

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

5.1.4. Full Analysis Set

FAS (Day 29)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide an evaluable serum sample at Day 29 that has an available result for serogroup A (primary objective)/ for at least one serogroup (secondary objectives). For percentages of subjects with a ≥4-fold rise, a baseline (Day 1) and a Day 29 result for at least one serogroup will be needed.

In case of vaccination error, subjects in the FAS set will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

5.1.5. Per Protocol (PP) Set for Immunogenicity Set

PPS (Day 29) is described as all subjects in the FAS (Day 29) who:

- correctly receive the vaccine (i.e., receive the vaccine to which the subject is randomized and at the scheduled time point).
- have no protocol deviations leading to exclusion as defined prior to unblinding.
- are not excluded due to other reasons defined prior to unblinding.

5.1.6. Other Analysis Sets

There are no additional analysis sets.

5.1.7. Subgroups

A subgroup analysis for GMTs, percentage of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 29, will be performed for subjects who were seronegative at baseline.

In addition, subgroup analyses will be performed for GMTs, four-fold rise, percentage of subjects with hSBA titer ≥8 and ≥LLOQ* by sex, by race and by country.

*Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

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 set.

A consolidated table is also available in Section 12 (Annex 2).

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Per Protocol Set (PPS)

5.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions (for more detailed exclusions by visit/day, refer to Section 12 (Annex 2).

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine not administered at all
1050	Randomization failure
1060	Randomization code was broken
1070	Subjects were vaccinated with the correct vaccine but containing a lower volume / Vaccination not according to protocol
1080	Vaccine temperature deviation
1090	Expired vaccine administered
1040	Administration of concomitant vaccine(s) forbidden in the protocol
2010	Protocol violation (inclusion/exclusion criteria)
2040	Administration of any medication forbidden by the protocol
2090	Subjects did not comply with blood sample schedule
2100	Serological results not available post-vaccination
2120	Obvious incoherence or abnormality or error in data

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Data from visit x will be censored for the PPS analysis under the following conditions. The code ****.x will also be used to identify study withdrawal from day y.

Code	Condition under which the code is used
2120.1	Obvious deviation from Laboratory Manual or error in the laboratory data at Day 1
2120.2	Obvious deviation from Laboratory Manual or error in the laboratory data at Day 29
2090.1	Subjects did not comply with blood sample schedule at Day 1
2090.2	Subjects did not comply with blood sample schedule at Day 29

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

Code 2150 (Subject did not provide any post-vaccination unsolicited safety data) and 2160 (Subject did not provide any post-vaccination solicited safety data) will be used for identifying subjects eliminated from Safety set.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and statistical methods are described in Section 11 (Annex 1) and will not be repeated below.

All statistical analyses will be carried out using SAS 9.3 or higher.

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 system organ class and verbatim term, by study group and overall.

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

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. Efficacy/Effectiveness

Not applicable

6.3.1. Analysis of efficacy planned in the protocol

Not applicable

6.3.2. Additional considerations

Not applicable

6.4. Immunogenicity

6.4.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the per-protocol set for analysis of immunogenicity. If, in any study group and timepoint, the percentage of vaccinated subjects with serological results excluded from the per-protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set will be performed to complement the per-protocol analysis.

GMTs, Between-group ratios of GMTs and within-group Geometric Mean Ratios (GMRs)

The hSBA titers at each visit will be logarithmically transformed (base10) to obtain approximately normally distributed data. For each *N. meningitidis* serogroup A, C, W and Y, GMTs will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

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

Within each study group and for each serogroup, GMRs will be calculated at Day 29 versus Day 1. The GMRs and 95% CIs will be constructed by exponentiating the within-group mean differences in log-transformed titers and the corresponding 95% CIs.

The mean differences will be obtained from an Analysis of Covariance (ANCOVA) including pre-vaccination titer (Day 1) as a covariate and with vaccine group and center (if applicable) as factors in the model.

Percentages of subjects with a ≥ 4-fold rise in post-vaccination hSBA (Day 29)

The percentage of subjects with a ≥ 4-fold rise in post-vaccination hSBA (at Day 29 compared to Day 1) and associated two-sided 95% Clopper-Pearson CIs will be computed by group and *N. meningitidis* serogroups A, C, W and Y. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen and Nurminen score method. [Clopper, 1934; Miettinen, 1985]

Percentage of Subjects with hSBA titer ≥8 and ≥LLOQ* (Day 1 and Day 29)

For each study group the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* and associated two-sided 95% Clopper-Pearson CIs will be computed by the *N. meningitidis* serogroups A, C, W and Y on Day 1 and Day 29. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen and Nurminen score method. [Clopper, 1934; Miettinen, 1985]

*Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

6.4.2. Additional considerations

The ANCOVA is used to adjust for the potential baseline imbalance between study groups. The ANCOVA analysis will be performed for the primary endpoint.

In addition, an Analysis of Variance (ANOVA) model with vaccine group and center (if applicable) as factors will be fitted in order to compute the estimates (not adjusted for pre-vaccination titer) together with their associated 95% CIs by exponentiating the corresponding log-transformed means and their 95% CIs.

For the 'by country' subgroup analysis, the ANCOVA and ANOVA models will be fitted without country in the model.

Given the high likelihood of having centers with few subjects enrolled in the study; therefore, country will be used as a factor in the ANCOVA/ANOVA analyses instead of center.

Permutation test (sensitivity analysis on primary objectives)

Based on the covariate-adaptive vaccine assignment algorithm (see Section 14 (Annex 4)), the following permutation test [Wiens, 2006; Hasegawa, 2009 and Ernst, 2004] will be performed as a sensitivity analysis on the primary objective in the PPS.

For serogroup A, let $\mathbf{X} = (X_1, \ldots, X_N)$ the logarithmically-transformed hSBA titers for the ACWY_liq group and $Y = (Y_1, \ldots, Y_N)$ the logarithmically-transformed hSBA titers for ACWY group at 1 month after vaccination. A non-inferiority permutation test can be obtained from a superiority permutation test on $\dot{\mathbf{X}} = (X_1 + \delta, \ldots, X_N + \delta)$ against $\dot{\mathbf{Y}} = (Y_1, \ldots, Y_N)$ with $\delta = 0.301 = -\log_{10}(0.5)$.

The original vaccine assignment algorithm Section 14 (Annex 4) will be used to re-randomize subjects belonging to the ACWY_Liq group and ACWY group (see step 2a) while keeping hSBA titers, covariates and entry order as observed. The procedure will be as follows:

1. Fit the ANCOVA model to obtain the test statistics **T*** for the superiority of $\dot{\mathbf{X}}$ against $\dot{\mathbf{Y}}$**;**
2. Estimate the distribution of the corresponding test statistic with R=10 000 repetitions of the following two steps:
   a. Re-randomize vaccine assignment of groups $\dot{\mathbf{X}}$ and $\dot{\mathbf{Y}}$ (original algorithm);
   b. Re-fit the full ANCOVA model to re-obtain the test statistics **T;**
3. Derive the permutation p-values associated with the observed test statistics (from Step 1) based on the empirical distributions in Step 2;

   p-value = M+1/R+1**,** where M is the number of repetitions such that **T≥T*.**

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

Safety analysis will be performed on the solicited safety set for solicited reactions and on unsolicited safety set for unsolicited adverse events.

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: Absent < 25 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”. The assessment of the intensity of solicited AEs is detailed in section 8.3.3.2.1 of the protocol.

Each solicited local and systemic adverse event will also be further summarized as “absent” 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 2 schemes described below and will be broken down according to route of measurements (axilla, oral cavity, rectum, tympanic membrane):

- 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.

Solicited AEs reported within 30 minutes post-vaccination will be summarized in a separate table.

Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as 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 per system organ class (SOC).

All reported adverse events, as well as adverse events judged by the investigator as at least related to study vaccine, will be summarized per SOC and preferred term within SOC. These summaries will be presented by study group and by interval of study observation (with onset from Day 1 through Day 29, during the follow-up period and throughout the study period). 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 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
- Adverse events leading to Death

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 (excluding Unsolicited AEs reported within 29 days after vaccination).

6.5.2. Additional considerations

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.

Incomplete/partial data in the e-Diary (e.g. local and/or systemic reactions reported only for some days and/or for some reactions) will not be considered as protocol deviations. Summary statistics for local and systemic adverse events will not include missing data, hence numerators and denominators may change from day to day and for the different reactions.

6.5.2.1. Exclusion of implausible solicited Adverse Event

This section is specific to the use of eDiary card. Exclusion from analyses due to implausible measurements is to be limited to measurements made by study subjects.

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 4 Implausible Solicited Adverse Events

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

6.5.2.2. Solicited Adverse Events

For details please refer to Section 8.1.3 of the protocol.

Fever, defined as a body temperature of ≥38°Cirrespective 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 (use of antipyretics and analgesics for treatment or prophylaxis), 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 any 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 (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: ≥ 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 (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 ≥ 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 "absent" (≥ 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.

Use of antipyretics and analgesics for treatment or prophylaxis to treat or prevent pain or fever will be summarized by frequencies and percentages of subjects reporting use of the medications by interval (6h - day 7).

6.5.2.3. Unsolicited Adverse Events

All AEs occurring during the first 29 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.

6.5.2.4. Combined Solicited and Unsolicited Adverse Events

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited (regardless of their duration) and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event. This analysis will be done on overall safety set.

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

6.5.2.5. Clinical Safety Laboratory Investigations

Not applicable

6.5.2.6. Concomitant Medication

Medications will be coded using the GlaxoSmithKline Drug Dictionary (GSKDRUG dictionary).

The frequencies and percentages of subjects starting/reporting concomitant medication within 29 days post-vaccination will be summarized overall and by study group.

7. ANALYSIS INTERPRETATION

7.1. Primary Immunogenicity Objective

The analysis population for the non-inferiority analysis is the Per Protocol Set (PPS).

To demonstrate non-inferiority of the investigational liquid MenACWY vaccines to the currently licensed MenACWY vaccine (*Menveo*), the lower limit of the two-sided 95% confidence interval (CI) for the hSBA GMT ratios for serogroup A at Day 29, must be greater than 0.5. Hypothesis testing will be performed at an overall significance level (α) of 2.5% (one-sided) using a non-inferiority margin of 0.5 for GMT ratios:

Null hypothesis (inferiority): $\mu_{\text{ACWY\_Liq30}} - \mu_{\text{ACWY}} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{\text{ACWY\_Liq30}} - \mu_{\text{ACWY}} > \log_{10}(0.5)$

Where: 0.5 is the non-inferiority margin for the ratio of GMTs between Group ACWY_Liq and Group ACWY; $\mu_{\text{ACWY\_Liq30}}$ and μ_{ACWY} are the population means of the logarithmically (base of 10) transformed titers for serogroup A in Group ACWY_Liq and Group ACWY, respectively.

If the lower limit of the two-sided 95% CI for the hSBA GMT ratio is greater than 0.5, then we conclude non-inferiority.

7.2. Secondary Immunogenicity Objectives

Analysis of secondary objectives will be descriptive.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in the protocol will be described and justified in the final study report.

8.1. Sequence of analyses

Only one analysis will be performed.

A CSR will be written and made available to the investigators.

Description	Analysis ID	Disclosure Purpose (CTRS=public 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 TFL
Final analysis	E1_01	SR and CTRS	Y	Yes	All tables from the latest TFL TOC in eTMF

8.2. Statistical considerations for interim analyses

No interim analysis is planned.

9. CHANGES FROM PLANNED ANALYSES

Planned interim analyses will not be performed; eCRF and lab data will be analyzed at the same time since the sera results release will be occur later than initially planned.

This modification has no impact from the statistical analysis perspective and all considerations about result interpretations remain valid and unchanged.

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 analysis and their role (synopsis, in-text, post-text, SHS, CTRS, etc.).

The mock tables referred under column named ‘layout’ can be found in GSK SDD dedicated folder for standard tables.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
1	Menveo Liquid	Subjects who received MenACWY- Liquid
2	Menveo	Subjects who received Licensed MenACWY

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

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

Ernst MD, Permutation Methods: A Basis for Exact Inference. *Statistical Science*, 2004; 19: 676-685.

Hasegawa T, Tango T. Permutation test Following Covariate-Adaptive Randomization in Randomized Controlled Trials. *Journal of Biopharmaceutical Statistics*, 2009; 19: 106-119.

Miettinen O., Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4(2):213-226.

Wiens BL, Randomization as basis for inference in noninferiority trials. *Pharmaceutical Statistics*, 2006; 5: 265-271

White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978; 37: 849-857

11.2. Standard data derivation

Immunogenicity

- A seronegative subject is a subject whose titer is below the LOD.
- A seropositive subject is a subject whose titer is greater than or equal to the LOD.
- Values below the limit of detection will be set to half that limit.
- Four-fold rise is defined as:
  - For individuals whose pre-vaccination titers are < LOD, the post-vaccination titers must ≥ max (4*LOD, LLOQ).
  - For individuals whose pre-vaccination titers are ≥ LOD and ≤ LLOQ, the post-vaccination titers ≥ 4*LLOQ.
  - For individuals whose pre-vaccination titers are > LLOQ, post-vaccination ≥ 4*pre-vaccination titer.
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Reactogenicity and Safety

- Handling of missing data: Subjects will be analyzed to the extent that they are 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 denominator for the time period in which they have no available safety data collected.

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 occurred 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 study vaccination (i.e., year or year & month is/are before the 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 study vaccination (i.e., year or year & month is/are after or the same as the 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 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 the second blood draw

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 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 frequencies and percentages of subjects will be summarized overall and by study group.

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Table 5 Safety Sets

PD code	*PD Description*	*Study Period*	*All Exposed Set*	*Overall Safety Set*	*Safety Set, Unsolicited AEs*	*Safety Set, Solicited AEs*
	Exclusion code		***EXPFL***	***SAFFL***	***SSUFL***	***SSSFL***
1030	***Study vaccine not administered AT ALL***	*Day 1 – Day 181*	*EXC*	*EXC*	*EXC*	*EXC*
2150	***Subject did not provide any post-vaccination unsolicited safety data***	*Day 1 – Day 181*	*None*	*None*	*EXC*	*None*
2160	***Subject did not provide any post-vaccination solicited safety data***	*Day 1- Day 7*	*None*	*None*	*None*	*EXC*

EXC = excluded from this analysis set.

Table 6 Immunogenicity Sets

PD code	**PD Description**	**Study Period**	***FAS Day 29***	***PP Day 29***
	Exclusion code		***FAS29FL***	***PPS29FL***
1030	**Study vaccine not administered AT ALL**	***All Study***	*EXC*	*EXC*
2100.1	***Serological results are not available at Day 1 for any of the serogroups***	Day 1	*EXC (for 4-fold rise only)*	*EXC (for 4-fold rise only)*
2100.2	***Serological results are not available at Day 29 for any of the serogroups***	Day 29	*EXC*	*EXC*
2120.1	***Obvious deviation from Laboratory Manual or error in laboratory data at Day 1 for any of the serogroups***	Day 1	*None*	*EXC (for 4-fold rise only)*
2120.2	***Obvious deviation from Laboratory Manual or error in laboratory data at Day 29***	Day 29	*None*	*EXC*
1050	**Randomization failure**	Day 1 – Day 29	*None*	*EXC*
1070	**Vaccination not according to protocol**	Day 1	*None*	*EXC*
1040	**Administration of forbidden vaccine**	Day 1 – Day 29	*None*	*EXC*
2010	**Subject did not meet entry criteria**	Day 1 – Day 29	*None*	*EXC*
2040	**Administration of forbidden medication**	Day 1 – Day 29	*None*	*EXC*
2090.1	**Day 1 blood draw performed out of planned visit window**	Day 1	*None*	*EXC (for 4-fold rise only)*
2090.2	**Day 29 blood draw performed out of planned visit window**	Day 29	*None*	*EXC*

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

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The summaries are to include the following header:

GSK Biologicals	Vaccine: MenACWY (GSK3536820A and *Menveo)*
MenACWY CONJ-032 [V59_71]	Immunogenicity and Safety in Healthy Individuals 18-40 years

14. ANNEX 4: RANDOMIZATION METHOD AND MINIMIZATION ALGORITHM

The minimization algorithm used at the GSK internet randomization system (i.e. SBIR) is based on the following reference: "White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study." [White, 1978] and is detailed in Section 14.1.

14.1. SBIR Algorithm V8.x

14.1.1. Introduction

This minimization algorithm is extracted from:

14.1.2. Minimization algorithm

14.1.2.1. Notations

- **K** input values to be used for minimization, each with a weight $\mathbf{w_k}$ ($\mathbf{k}$=1,.., K) & $\mathbf{l_k}$ variants
- **I** treatment groups applicable to stratum the subject has been identified with randomization ratio $\mathbf{a_1}$,… $\mathbf{a_I}$

14.1.2.2. Algorithm

For a new subject with input value levels S_1,…. S_K

For each input value variants **sk**:

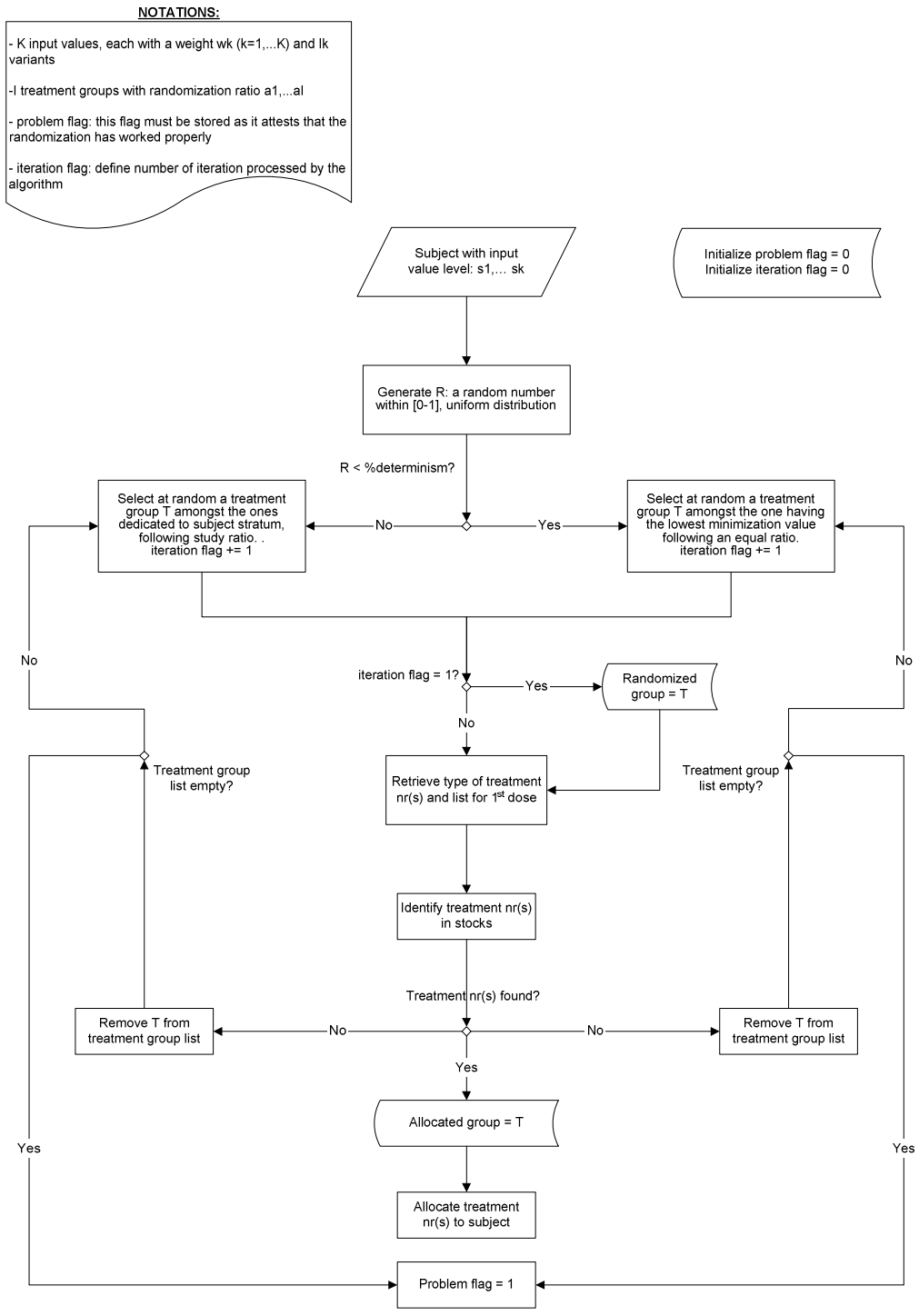
- Compute the number of subjects already enrolled in each treatment in the identified stratum.
  - Let **bik** the total number of subjects in the identified stratum already randomized in treatment **I** and in input value variant **k**.

For each treatment **i**: compute $\mathbf{A_i} = 1/\mathbf{a_i} * \text{sum}_k(\mathbf{w_k}*\mathbf{b_{ik}})$

Where $\mathbf{A_i}$ is the minimization value for treatment **i**.

14.1.3. Study group selection

14.1.3.1. Process flow



14.1.3.2. Study Group identification algorithm

The seed used to initialize randomization engine must take into account date time till microsecond, this will ensure uniqueness of the seed for each subject.

This seed is to be recorded along with randomization data of the subject.

1. **Determine whether the algorithm is deterministic or not:**

- Generate R, a random number within [0-1], uniform distribution.
- **If** R < % determinism parameter

  then

  group allocation will be deterministic go to (2)

  else

  it will be at random go to (3).

2. **Group allocation is deterministic:**

- Order treatment groups, which can be allocated to the subject according to his stratum, by minimization value,
- If more than 1 group have the same minimization value then select at random a treatment group amongst them, randomization ratio must be equal for each of these groups.
- If this is the 1st iteration then this group is identified as the "randomized" group,
- Go to step (4).

3. **Group allocation is at random:**

- Retrieve list of treatment groups and ratio which can be allocated to the subject according to his stratum,
- Select at random one of the treatment groups, randomization must follow study ratio.
- If this is the 1st iteration then this group is identified as the "randomized" group.

4. **Check for treatment No(s). dedicated to the 1st vaccination time point for the selected treatment group.**

- Check vaccination schedule of the selected group for the subject's stratum in order to identify:
  - the type of treatment No(s) to be allocated
  - the list from which these treatment No(s) should be extracted depending if center using ordering system or not.

- For each type of treatment for which a treatment No. must be identified:
  - The treatment No(s) to be selected must have an expiry date greater than the planned vaccination date entered for subject.
  - In case multiple injections can be extracted from 1 treatment No. then first used the "opened" treatment Nos.
  - The treatment Nos. must be selected starting by the ones expiring first, then by the one first received in the stock to be used for allocation, then on the block id's.
  - In case "Ordering system" is activated on the center without "Randomization pool", check the stock according to below order:
    i. Center stock
  - In case "Ordering system" is activated on the center with "Randomization pool", check the stock according to below order:
    i. Randomization pool
  - In case "Ordering system" is not activated on the center, check the stock in according to below order:
    i. Center stock
  - All the treatment No(s) to be allocated to the subject must be issued from the same stock.

5. **If it was not possible to allocate all the necessary treatment No(s) from the stocks, then :**

- The identified treatment No(s) are sent back to the stock they have been identified
- The selected treatment group is removed from the possible treatment group
- If there are still treatment group on which to iterate,

  then

  algorithm must start new iteration at (2 or 3, depending on determinism),

  else

  an error message must be issued.

  Else:
- The selected treatment group is identified as the "allocated" group.

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase 2b, randomized, controlled, observer-blind, multi-center, non-inferiority immunogenicity and safety study of two formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) administered to healthy adults 18 to 40 years of age.
eTrack study number and Abbreviated Title	205343 (MENACWY CONJ-032 [V59_71])
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 29 AUG 2018
Co-ordinating author:	PPD (Biostatistician)
Reviewed by:	PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Clinical and Epidemiology Research and Development Project Lead) PPD (Clinical Research and Development Lead) PPD (Scientific writer) PPD (Regulatory Affairs representative) PPD (Clinical Safety representative) PPD (Public disclosure representative)
Approved by:	PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Clinical and Epidemiology Research and Development Project Lead) PPD (Clinical Research and Development Lead) PPD (Scientific writer)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BSP	BioStatistics and Statistical Programming
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EoS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
GSKDRUG	GlaxoSmithKline Drug Dictionary
hSBA	Human Serum Bactericidal Assay
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
LOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N. meningitidis	*Neisseria meningitidis*
PCD	Primary Completion Date
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings

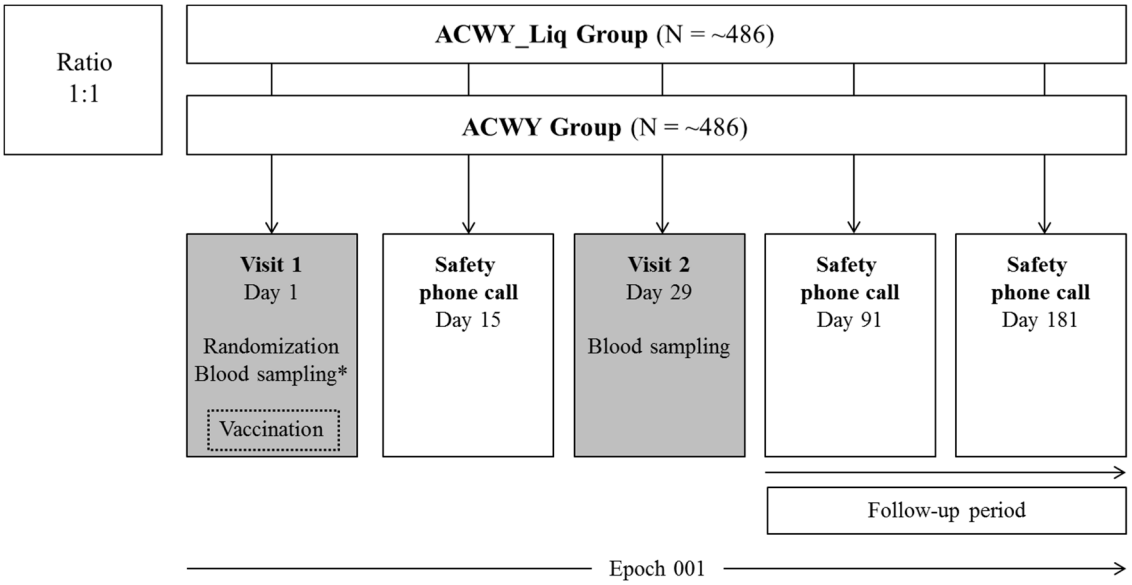
TOC	Table of Content
UL	Upper Limit of the confidence interval
YoA	Years of Age

1. DOCUMENT HISTORY

Date	Description	Protocol Version
29-AUG-2018	First version	Protocol Amendment 2: 15-MAR-2018

2. STUDY DESIGN

Figure 1 Study design overview



* At Visit 1, blood samples will be taken pre-vaccination

- Experimental design: Phase IIB, observer-blind, randomized, controlled, multi-centric study with two parallel groups.
- Duration of the study: for each subject enrolled, the duration will be approximately 6 months.
  - Epoch 001: starting at Visit 1 (Day 1) and ending at last Safety contact (Day 181).
- Primary completion Date (PCD): Visit 2 (Day 29).
- End of Study (EoS): Last subject last visit(LSLV) (Phone call 3 - Day 181) or last testing results released of samples collected at Visit 2 (Day 29)* if it occurs after LSLV.

  *In this case EoS must be achieved no later than 8 months after LSLV.
- Study groups:
  - **Group ACWY_Liq**: ~486 healthy adults receiving a single dose of investigational liquid MenACWY (GSK3536820A) with approximately 30% Men A FS.

– **Group ACWY**: ~486 healthy adults receiving a single dose of currently licensed GSK' MenACWY vaccine (Menveo).

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
ACWY_Liq	~486	18 – 40 years	x
ACWY	~486	18 – 40 years	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/product name	Study Groups	
		ACWY_Liq	ACWY
MenACWY liquid with approximately 30% MenA FS	MenACWY liquid	x	
Licensed MenACWY (*Menveo**)	MenA lyo		x
	MenCWY liquid		

* *Menveo* commercial formulation consisting of a MenA lyophilized component and a MenCWY liquid component to be reconstituted together before administration (0.5mL).

- Control: active control
- Vaccination schedule: All subjects will receive a single dose of one of the study vaccines at Visit 1 (Day 1).
- Treatment allocation: Subjects will be randomized using a centralized randomization system on internet (SBIR) at Visit 1 (Day 1).
- Blinding: observer-blind.
- Sampling schedule: Blood samples of approximately 20 mL will be taken at Visit 1 (Day 1; pre-vaccination) and Visit 2 (Day 29).
- Type of study: self-contained.
- Data collection: Standardised Electronic Case Report Form (eCRF). Solicited adverse events (AEs) assessed on site during the 30 minutes post-vaccination assessment are to be recorded on the source documents and entered in the eCRF. Solicited AEs occurring after the 30 minutes post-vaccination assessment will be collected only using a subject Diary (electronic Diary [eDiary]).

Table 3 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Visit 1 → Phone call 1	14 days	11 - 17 days
Visit 1 → Visit 2	28 days	21 - 42 days
Visit 1 → Phone call 2	90 days	76 - 104 days
Visit 1 → Phone call 3	180 days	166 - 194 days

3. OBJECTIVES

3.1. Primary objective

- To demonstrate non-inferiority of the investigational liquid MenACWY vaccine with approximately 30% Men A FS to that of currently licensed MenACWY vaccine, as measured by the human serum bactericidal assay (hSBA) Geometric Mean Titers (GMTs) directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  Criterion to demonstrate non-inferiority:

  Non-inferiority will be concluded if the lower limit of the two-sided 95% confidence interval (CI) for the ratio of hSBA GMTs against serogroup A between the liquid formulation and the licensed formulation is greater than 0.5.

3.2. Secondary objectives

- To compare the immunogenicity of the investigational liquid MenACWY vaccine with approximately 30% Men A FS and the currently licensed MenACWY vaccine, as measured by hSBA GMTs directed against *N. meningitidis* serogroups C, W and Y at Day 29.
- To compare the immunogenicity of the investigational liquid MenACWY vaccine with approximately 30% Men A FS to the currently licensed MenACWY vaccine, as measured by the percentage of subjects with a ≥ 4-fold rise in post vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1.

  Note: The following definition will be used for 4-fold rise: a) for individuals whose pre-vaccination titers are < the limit of detection (LOD), the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the lower limit of quantitation (LLOQ) whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post vaccination titers must be at least four times the pre-vaccination titer.
- To compare the immunogenicity of the investigational liquid MenACWY vaccine with approximately 30% Men A FS to the currently licensed MenACWY vaccine, as measured by the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 29.

  *Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.
- To assess the safety/reactogenicity of the investigational liquid MenACWY vaccines with approximately 30% Men A FS and the currently licensed MenACWY vaccine.

4. ENDPOINTS

4.1. Primary endpoint

The following measures will be summarized:

- hSBA GMTs against N. meningitidis serogroup A at Day 29, for each vaccine group and between-group ratios.

4.2. Secondary endpoints

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroups A (except Day 29), C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group ratios.
- Within-group ratios of hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1.
- Percentages of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer for *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group and between-group differences.

  Note: A 4-fold rise is defined as: a) for individuals whose pre-vaccination titers are < the LOD, the post-vaccination titers must be ≥ 4-fold the LOD or ≥ the LLOQ whichever is greater; b) for individuals whose pre-vaccination titers are ≥ the LOD and ≤ the LLOQ, the post-vaccination titers must be at least four times the LLOQ; c) for individuals whose pre-vaccination titers are > the LLOQ, the post-vaccination titers must be at least four times the pre-vaccination titer.
- Percentages of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 1 and at Day 29, for each vaccine group and between-group differences.

  *Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

Safety of the study vaccine formulations will be evaluated for all vaccine groups in terms of the frequency (percentage) of reported adverse events including:

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

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 Set

5.1.3.1. Solicited Safety Set (solicited local and systematic adverse events and other solicited adverse events)

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

5.1.3.2. Unsolicited Safety Set (unsolicited adverse events)

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

5.1.3.3. Overall Safety Set

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

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

5.1.4. Full Analysis Set

FAS (Day 29)

All subjects in the All Enrolled Set who:

- are randomized;
- receive the study vaccination;
- provide an evaluable serum sample at Day 29 that has an available result for serogroup A (primary objective)/ for at least one serogroup (secondary objectives). For percentages of subjects with a ≥4-fold rise, a baseline (Day 1) and a Day 29 result for at least one serogroup will be needed.

In case of vaccination error, subjects in the FAS set will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

5.1.5. Per Protocol (PP) Set for Immunogenicity Set

PPS (Day 29) is described as all subjects in the FAS (Day 29) who:

- correctly receive the vaccine (i.e., receive the vaccine to which the subject is randomized and at the scheduled time point).
- have no protocol deviations leading to exclusion as defined prior to unblinding.
- are not excluded due to other reasons defined prior to unblinding.

5.1.6. Other Analysis Sets

There are no additional analysis sets.

5.1.7. Subgroups

A subgroup analysis for GMTs, percentage of subjects with hSBA titer ≥8 and ≥LLOQ* against *N. meningitidis* serogroups A, C, W and Y at Day 29, will be performed for subjects who were seronegative at baseline.

In addition, subgroup analyses will be performed for GMTs, four-fold rise, percentage of subjects with hSBA titer ≥8 and ≥LLOQ* by sex, by race and by country.

*Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

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 set. Add the text in blue if applicable.

A consolidated table is also available in Annex 2.

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Per Protocol Set (PPS)

5.2.2.1. Excluded subjects

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

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine not administered at all
1050	Randomization failure
1060	Randomization code was broken
1070	Subjects were vaccinated with the correct vaccine but containing a lower volume / Vaccination not according to protocol
1080	Vaccine temperature deviation
1090	Expired vaccine administered
1040	Administration of concomitant vaccine(s) forbidden in the protocol
2010	Protocol violation (inclusion/exclusion criteria)
2040	Administration of any medication forbidden by the protocol
2090	Subjects did not comply with blood sample schedule
2100	Serological results not available post-vaccination
2120	Obvious incoherence or abnormality or error in data

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Data from visit x will be censored for the PPS analysis under the following conditions. The code ****.x will also be used to identify study withdrawal from day y.

Code	Condition under which the code is used
2120.1	Obvious deviation from Laboratory Manual or error in the laboratory data at Day 1
2120.2	Obvious deviation from Laboratory Manual or error in the laboratory data at Day 29
2090.1	Subjects did not comply with blood sample schedule at Day 1
2090.2	Subjects did not comply with blood sample schedule at Day 29

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

Code 2150 (Subject did not provide any post-vaccination unsolicited safety data) and 2160 (Subject did not provide any post-vaccination solicited safety data) will be used for identifying subjects eliminated from Safety set.

6. STATISTICAL ANALYSES

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

All statistical analyses will be carried out using SAS 9.3 or higher.

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 system organ class and verbatim term, by study group and overall.

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

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. Efficacy/Effectiveness

Not applicable

6.3.1. Analysis of efficacy planned in the protocol

Not applicable

6.3.2. Additional considerations

Not applicable

6.4. Immunogenicity

6.4.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the per-protocol set for analysis of immunogenicity. If, in any study group and timepoint, the percentage of vaccinated subjects with serological results excluded from the per-protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set will be performed to complement the per-protocol analysis.

GMTs, Between-group ratios of GMTs and within-group Geometric Mean Ratios (GMRs)

The hSBA titers at each visit will be logarithmically transformed (base10) to obtain approximately normally distributed data. For each *N. meningitidis* serogroup A, C, W and Y, GMTs will be calculated, with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

The between-group ratio of hSBA GMTs and corresponding 95% CI, at each of Day 1 and Day 29 against *N. meningitidis* serogroups A, C, W and Y will be obtained by

exponentiating the between-group mean differences in log-transformed titers and the corresponding 95% CIs at each of the specified timepoints.

Within each study group and for each serogroup, GMRs will be calculated at Day 29 versus Day 1. The GMRs and 95% CIs will be constructed by exponentiating the within-group mean differences in log-transformed titers and the corresponding 95% CIs.

The mean differences will be obtained from an Analysis of Covariance (ANCOVA) including pre-vaccination titer (Day 1) as a covariate and with vaccine group and center (if applicable) as factors in the model.

Percentages of subjects with a ≥ 4-fold rise in post-vaccination hSBA (Day 29)

The percentage of subjects with a ≥ 4-fold rise in post-vaccination hSBA (at Day 29 compared to Day 1) and associated two-sided 95% Clopper-Pearson CIs will be computed by group and *N. meningitidis* serogroups A, C, W and Y. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen and Nurminen score method.

Percentage of Subjects with hSBA titer ≥8 and ≥LLOQ* (Day 1 and Day 29)

For each study group the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* and associated two-sided 95% Clopper-Pearson CIs will be computed by the *N. meningitidis* serogroups A, C, W and Y on Day 1 and Day 29. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen and Nurminen score method.

*Note: To be assessed for each serogroup if the pre-defined LLOQ value for that serogroup is >8.

6.4.2. Additional considerations

The ANCOVA is used to adjust for the potential baseline imbalance between study groups. The ANCOVA analysis will be performed for the primary endpoint.

In addition, an Analysis of Variance (ANOVA) model with vaccine group and center (if applicable) as factors will be fitted in order to compute the estimates (not adjusted for pre-vaccination titer) together with their associated 95% CIs by exponentiating the corresponding log-transformed means and their 95% CIs.

For the 'by country' subgroup analysis, the ANCOVA and ANOVA models will be fitted without country in the model.

Given the high likelihood of having centers with few subjects enrolled in the study; therefore country will be used as a factor in the ANCOVA/ANOVA analyses instead of center.

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

Safety analysis will be performed on the solicited safety set for solicited reactions and on unsolicited safety set for unsolicited adverse events.

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: Absent < 25 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”. The assessment of the intensity of solicited AEs is detailed in section 8.3.3.2.1 of the protocol.

Each solicited local and systemic adverse event will also be further summarized as “absent” 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 measurements (axilla, oral cavity, rectum, tympanic membrane):

- 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 per 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 per SOC and preferred term within SOC. These summaries will be presented by study group and by interval of study observation (with onset from Day 1 through Day 29, during the follow-up period and throughout the study period). 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
- Adverse events leading to Death

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 (excluding Unsolicited AEs reported within 29 days after vaccination).

6.5.2. Additional considerations

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.

6.5.2.1. Exclusion of implausible solicited Adverse Event

This section is specific to the use of eDiary card. Exclusion from analyses due to implausible measurements is to be limited to measurements made by study subjects.

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 4 Implausible Solicited Adverse Events

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

6.5.2.2. Solicited Adverse Events

For details please refer to Section 8.1.3 of the protocol.

Fever, defined as a body temperature of ≥38°Cirrespective 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 (use of antipyretics and analgesics for treatment or prophylaxis), 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 any 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 (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: ≥ 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 (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 ≥ 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 "absent" (≥ 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.

Use of antipyretics and analgesics for treatment or prophylaxis to treat or prevent pain or fever will be summarized by frequencies and percentages of subjects reporting use of the medications by interval (6h - day 7).

6.5.2.3. Unsolicited Adverse Events

All AEs occurring during the first 29 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.

6.5.2.4. Combined Solicited and Unsolicited Adverse Events

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited (regardless of their duration) and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event. This analysis will be done on overall safety set.

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

6.5.2.5. Clinical Safety Laboratory Investigations

Not applicable

6.5.2.6. Concomitant Medication

Medications will be coded using the GlaxoSmithKline Drug Dictionary (GSKDRUG dictionary).

The frequencies and percentages of subjects starting/reporting concomitant medication within 29 days post-vaccination will be summarized overall and by study group.

7. ANALYSIS INTERPRETATION

7.1. Primary Immunogenicity Objective

The analysis population for the non-inferiority analysis is the Per Protocol Set (PPS).

To demonstrate non-inferiority of the investigational liquid MenACWY vaccines to the currently licensed MenACWY vaccine (*Menveo*), the lower limit of the two-sided 95% confidence interval (CI) for the hSBA GMT ratios for serogroup A at Day 29, must be greater than 0.5. Hypothesis testing will be performed at an overall significance level (α) of 2.5% (one-sided) using a non-inferiority margin of 0.5 for GMT ratios:

Null hypothesis (inferiority): $\mu_{\text{ACWY\_Liq30}} - \mu_{\text{ACWY}} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{\text{ACWY\_Liq30}} - \mu_{\text{ACWY}} > \log_{10}(0.5)$

Where: 0.5 is the non-inferiority margin for the ratio of GMTs between Group ACWY_Liq and Group ACWY; $\mu_{\text{ACWY\_Liq30}}$ and μ_{ACWY} are the population means of the logarithmically (base of 10) transformed titers for serogroup A in Group ACWY_Liq and Group ACWY, respectively.

If the lower limit of the two-sided 95% CI for the hSBA GMT ratio is greater than 0.5, then we conclude non-inferiority.

7.2. Secondary Immunogenicity Objectives

Analysis of secondary objectives will be descriptive.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in the protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The analysis will be performed in the following steps:

- An interim analysis will be performed after the availability of the Visit 2 (Day 29) immunogenicity and safety data. The analysis of immunogenicity and safety data collected up to Day 29 (Visit 2) might be reported in an interim clinical study report (CSR) for regulatory purposes.
- The analyses of safety data received after Visit 2 (Day 29) until study end (Day 181) will be performed at the end of the study when all data are available and cleaned.

An integrated CSR including the interim and the final analyses will be written and made available to the investigators.

Description	Analysis ID	Disclosure Purpose (CTRS=public 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 TFL
Interim analysis	E1_01	SR	Y	Yes	All tables from TFL dated 29-AUG-2018
Final analysis	E1_02	SR and CTRS	Y	Yes	All tables from TFL dated 29-AUG-2018

8.2. Statistical considerations for interim analyses

The interim and final analyses will be performed sequentially. An interim analysis will include analyses of the primary and secondary endpoints and safety data. The analysis will be performed after the availability of the Visit 2 immunogenicity and safety data.

The results of the interim analysis will provide information to plan the study design for a Phase 3 study.

An interim analysis will be performed by the BioStatistics and Statistical Programming (BSP) department. It will follow this current SAP and its corresponding TOC. To ensure that the study team remains blinded during the conduct of the trial, only the blinded data listings will be prepared (to assess subjects to be excluded from the analyses) together with summary tables.

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, CTRS, etc.).

The mock tables referred under column named ‘layout’ can be found in GSK SDD dedicated folder for standard tables.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
1	Menveo Liquid	Subjects who received MenACWY-Liquid
2	Menveo	Subjects who received Licensed MenACWY

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL 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

- A seronegative subject is a subject whose titer is below the LOD.
- A seropositive subject is a subject whose titer is greater than or equal to the LOD.
- Values below the limit of detection will be set to half that limit.
- Four-fold rise is defined as:
  - For individuals whose pre-vaccination titers are < LOD, the post-vaccination titers must ≥ max (4*LOD, LLOQ).
  - For individuals whose pre-vaccination titers are ≥ LOD and ≤ LLOQ, the post-vaccination titers ≥ 4*LLOQ.
  - For individuals whose pre-vaccination titers are > LLOQ, post-vaccination ≥ 4*pre-vaccination titer.
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Reactogenicity and Safety

- Handling of missing data: Subjects will be analyzed to the extent that they are 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 denominator for the time period in which they have no available safety data collected.

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 occurred 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 study vaccination (i.e., year or year & month is/are before the 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 study vaccination (i.e., year or year & month is/are after or the same as the 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 the second blood draw

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 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 frequencies and percentages of subjects will be summarized overall and by study group.

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Table 5 Safety Sets

PD code	*PD Description*	*Study Period*	*All Exposed Set*	*Overall Safety Set*	*Safety Set, Unsolicited AEs*	*Safety Set, Solicited AEs*
	Exclusion code		***EXPFL***	***SAFFL***	***SSUFL***	***SSSFL***
1030	***Study vaccine not administered AT ALL***	*Day 1 – Day 181*	*EXC*	*EXC*	*EXC*	*EXC*
2150	***Subject did not provide any post-vaccination unsolicited safety data***	*Day 1 – Day 181*	*None*	*None*	*EXC*	*None*
2160	***Subject did not provide any post-vaccination solicited safety data***	*Day 1- Day 7*	*None*	*None*	*None*	*EXC*

EXC = excluded from this analysis set.

Table 6 Immunogenicity Sets

PD code	**PD Description**	**Study Period**	***FAS Day 29***	***PP Day 29***
	Exclusion code		***FAS29FL***	***PPS29FL***
1030	**Study vaccine not administered AT ALL**	***All Study***	*EXC*	*EXC*
2100.1	***Serological results are not available at Day 1 for any of the serogroups***	Day 1	*EXC (for 4-fold rise only)*	*EXC (for 4-fold rise only)*
2100.2	***Serological results are not available at Day 29 for any of the serogroups***	Day 29	*EXC*	*EXC*
2120.1	***Obvious deviation from Laboratory Manual or error in laboratory data at Day 1 for any of the serogroups***	Day 1	*None*	*EXC (for 4-fold rise only)*
2120.2	***Obvious deviation from Laboratory Manual or error in laboratory data at Day 29***	Day 29	*None*	*EXC*
1050	**Randomization failure**	Day 1 – Day 29	*None*	*EXC*
1070	**Vaccination not according to protocol**	Day 1	*None*	*EXC*
1040	**Administration of forbidden vaccine**	Day 1 – Day 29	*None*	*EXC*
2010	**Subject did not meet entry criteria**	Day 1 – Day 29	*None*	*EXC*
2040	**Administration of forbidden medication**	Day 1 – Day 29	*None*	*EXC*
2090.1	**Day 1 blood draw performed out of planned visit window**	Day 1	*None*	*EXC (for 4-fold rise only)*
2090.2	**Day 29 blood draw performed out of planned visit window**	Day 29	*None*	*EXC*

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

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The summaries are to include the following header:

GSK Biologicals	Vaccine: MenACWY (GSK3536820A and *Menveo)*
MenACWY CONJ-032 [V59_71]	Immunogenicity and Safety in Healthy Individuals 18-40 years