GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase 2b, randomized, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) administered to healthy adolescents and young adults 10 to 40 years of age.
eTrack study number and Abbreviated Title	207467 (MENACWY CONJ-069 [V59_78])
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 13 August 2018 Amendment 1 Final: 11 July 2019
Co-ordinating author:	PPD (Lead Statistician)
Reviewed by:	PPD (Director, Biostatistics) 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 (Director, Biostatistics) 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)

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LIST OF ABBREVIATIONS

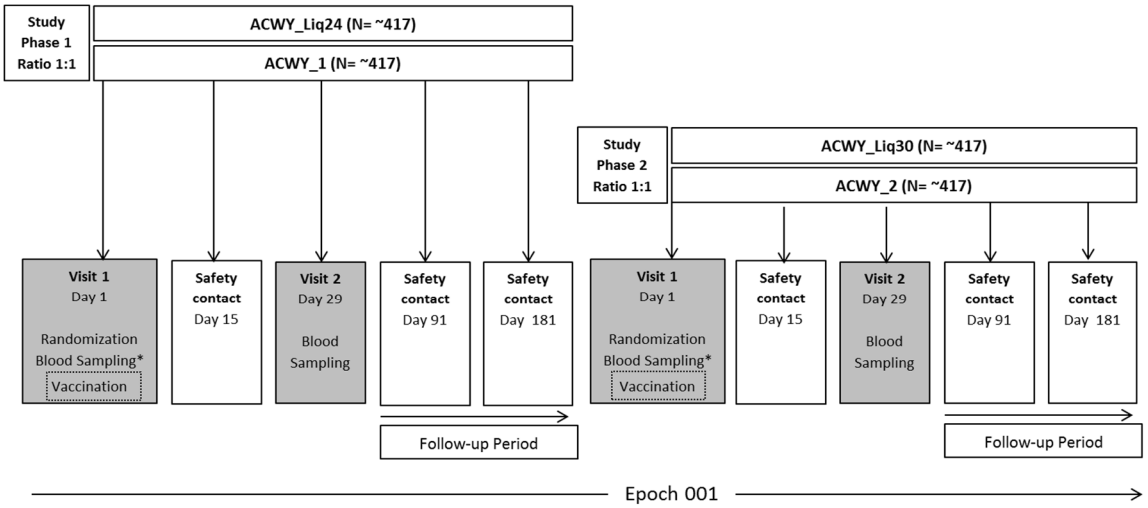
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BSP	BioStatistics and Statistical Programming
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EoS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
GSKDRUG	GlaxoSmithKline Drug Dictionary
hSBA	Human Serum Bactericidal Assay
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantitation
LOD	Lower Limit of Detection
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
N. meningitidis	*Neisseria meningitidis*
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomization System
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
13 AUG 2018	First Version	Amendment 2 Final: 15 MAR 2018
11 JUL 2019	Amendment 1 Final, list of changes: • Addition of solicited safety set at 30' post vaccination (5.1.3.2) • Addition of permutation test and sensitivity analysis on primary objective (6.4.2) • Addition of analysis of solicited AEs at 30' (6.5.1) • Sequence of analysis update (8.1) • Removal of interim analysis as no longer applicable (8.2) • Changed from planned analysis (9.8) • Addition of details for Randomization method and minimization algorithm (10.1) • To specify that V16 of TOC will be used	Amendment 3 Final: 08 FEB 2019

2. STUDY DESIGN

Figure 1 Study design overview



*Blood sample collection from Visit 1 will be performed before vaccine administration

- Experimental design: Phase IIB, observer-blind, randomized, controlled, multi-centric study with two parallel groups per phase, in a two phases staggered design.
- Duration of the study: The duration of this study is approximately 6 months per subject.
  - 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) of Study Phase 2* if it occurs after LSLV.

  * In this case EoS must be achieved no later than 8 months after LSLV.
- Study groups:
  - **ACWY_Liq24** (Study Phase 1): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 24 months at 2-8ºC;
  - **ACWY_1** (Study Phase 1): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (*Menveo*), not aged;
  - **ACWY_Liq30** (Study Phase 2): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 30 months at 2-8ºC;
  - **ACWY_2** (Study Phase 2): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (*Menveo*), not aged.

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
ACWY_Liq24*	417	10 years – 40 years	x
ACWY_1	417	10 years – 40 years	x
ACWY_Liq30**	417	10 years – 40 years	x
ACWY_2	417	10 years – 40 years	x

* ACWY_Liq24: vaccine lot aged for approximately 24 months.
** ACWY_Liq30: vaccine lot aged for approximately 30 months.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/product name	Study Groups			
		ACWY_Liq24	ACWY_1	ACWY_Liq30	ACWY_2
MenACWY Liquid	MenACWY Liquid	x		x	
Licensed MenACWY (*Menveo**)	MenA lyo MenCWY liquid		x		x

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

- Control: active control.
- Vaccination schedule: All subjects will receive a single dose of study vaccine at Visit 1 (Day 1).
- Treatment allocation: Randomization will be performed at Visit 1 (Day 1) using a central randomization system on the internet (SBIR), with stratification to include 40% of subjects from ≥10 to <18 YoA and 60% from ≥18 to ≤40 YoA.

- Blinding: observer-blind for each of the two phases of the study.
- Sampling schedule: Blood sample of approximately 20 ml will be collected from each subject at Visit 1 (Day 1; pre-vaccination) and at 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 using a subject Diary (electronic Diary [eDiary]).

3. OBJECTIVES

3.1. Primary objectives

- To demonstrate non-inferiority of the investigational MenACWY liquid product aged for approximately 24 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  Criterion:

  Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 24 months and the licensed MenACWY vaccine is greater than 0.5.

- To demonstrate non-inferiority of the investigational MenACWY liquid vaccine aged for approximately 30 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  Criterion:

  Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 30 months and the licensed MenACWY vaccine is greater than 0.5.

Non-inferiority hypotheses testing will be conducted sequentially, starting from vaccine lot aged for approximately 24 months and subsequently with vaccine lot aged for approximately 30 months.

3.2. Secondary objectives

- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months 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 MenACWY liquid products aged for approximately 24 or 30 months and 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: A 4-fold rise is defined as: 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; and 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 MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* directed 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 MenACWY liquid vaccine aged approximately 24 or 30 months and the currently licensed MenACWY vaccine.

4. ENDPOINTS

4.1. Primary endpoints

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroup A at Day 29, for each vaccine group and between-group ratios (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

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 (between vaccine serogroups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).
- Within-group ratios of hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group.
- 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 (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

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 (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2)

  * 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) 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 (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 Day 1 – Day 7 (solicited local and systemic 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' (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data reported at site within 30' post vaccination.

5.1.3.1.2. Solicited Safety Set 6 hours – Day 7 (solicited local and systemic adverse events and other solicited adverse events)

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

5.1.3.1.3. Unsolicited Safety Set (unsolicited adverse events)

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

5.1.3.2. 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) for immunogenicity

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 ≥ 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 sets 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

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 / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis

PPS are subsets of FAS and should be always defined even if the objectives do not require it.

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

- Subjects who withdrew informed consent.

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, by country and by age group (≥10 to <18 YoA and ≥18 to ≤40 YoA).

*Note: To be assessed for each serogroup if the pre-defined LLOQ value for the 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 analysis 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

The code ****.X will be used to identify study withdrawal from visit X.

Code	Condition under which the code is used
2120.1	Obvious deviation from Laboratory Manual or error in the laboratory data at Visit 1
2120.2	Obvious deviation from Laboratory Manual or error in the laboratory data at Visit 2
2090.1	Subjects did not comply with blood sample schedule at Visit 1
2090.2	Subjects did not comply with blood sample schedule at Visit 2

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

Codes 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 sets.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat 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, age group 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, PPS (Day 29), FAS (Day 29) and Overall Safety set, by 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 FAS 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 mean between-group differences in log-transformed titers and the corresponding 95% CIs at each of the specified timepoints. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

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 mean within-group 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 country as factors in the model.

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

The percentage of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer (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 [Clopper, 1934]. Differences in percentages and associated 95% CIs between study groups will be calculated using the Miettinen and Nurminen score method [Miettinen, 1985]. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

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. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

* 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) with vaccine group and country as factors in the model 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.

Given the 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. A sensitivity analysis will be performed for the primary endpoint, including the age group (≥10 to <18 YoA and ≥18 to ≤40 YoA) as additional factor in the same ANCOVA model with pre-vaccination titer (Day 1) as a covariate and vaccine group and country as factors.

Permutation test (sensitivity analysis on primary objectives)

Based on the covariate-adaptive treatment assignment algorithm (see Section 10.1), the following permutation test will be performed as a sensitivity analysis on the primary objectives [Wiens, 2006; Hasegawa, 2009 and Ernst, 2004] in the PPS.

For serogroup A, let $\mathbf{X} = (X_1, \ldots, X_N)$ the logarithmically-transformed hSBA titers for the ACWY_Liq24 group and $\mathbf{Y}=(Y_1, \ldots, Y_N)$ the logarithmically-transformed antibody concentrations for ACWY_1 at Day 29. 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 will be used to re-randomize subjects belonging to the ACWY_Liq24 group and to the ACWY_1 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 statistics with R=10000 repetitions of the following 2 steps:
   a. Re-randomize treatment 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 to the observed test statistics (from step 1) based on the empirical distributions in Step 2; **p** = M+1/R+1, where M is the number of repetitions such that $T \geq T^*$.

The same sensitivity analysis will be repeated for Phase 2 ACWY_Liq30 and ACWY_2 groups.

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 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 measurement (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.

Solicited Adverse Events as reported at site within 30' post vaccination will be shown 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 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 (with onset from Day 1 through Day 29 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

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 3 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°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 (use of antipyretics and analgesics for treatment/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 "none" (≥ 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 (to treat or to prevent pain/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 performed on the 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 GSKDRUG dictionary.

The frequencies and percentages of subjects starting/reporting concomitant medications within 29 days post-vaccination will be tabulated 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 MenACWY liquid 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. Hierarchical hypothesis testing will be performed at overall Type I Error of 2.5% (one-sided) using non-inferiority margin of 0.5 for GMT ratios.

The two hypotheses will be tested sequentially as follows:

1. Group ACWY_Liq24 versus Group ACWY_1

Null hypothesis (inferiority): $\mu_{\text{ACWY\_Liq24}} - \mu_{\text{ACWY\_1}} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{\text{ACWY\_Liq24}} - \mu_{\text{ACWY\_1}} > \log_{10}(0.5)$

Where: 0.5 is the non-inferiority margin for the ratio of GMTs between Group ACWY_Liq24 and Group ACWY_1; $\mu_{\text{ACWY_Liq2}}$and $\mu_{\text{ACWY\_}}$ are the population means of the logarithmically (base of 10) transformed titers for serogroup A in Group ACWY_Liq24 and Group ACWY_1, 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 and proceed to test the next hypothesis for Group ACWY_Liq30 versus Group ACWY_2. Otherwise, further hypothesis testing is not conducted.

2. Group ACWY_Liq30 versus Group ACWY_2

Null hypothesis (inferiority): $\mu_{\text{ACWY\_Liq30}} - \mu_{\text{ACWY\_2}} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{\text{ACWY\_Liq30}} - \mu_{\text{ACWY\_2}} > \log_{10}(0.5)$

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 this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The analysis will be performed in two steps, phase 1 first and, subsequently, Phase 2:

- Phase 1: all data (CRF and lab) will be analysed and reported in a clinical study report (CSR) for regulatory purposes. This report will be named "Interim Study Report".
- Phase 2: all data (CRF and lab) will be analysed and reported in an integrated CSR including Phase 1 and Phase 2 analysis and made available to the investigators. This final report will be named "Integrated Study Report".

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
Phase 1	E1_01	SR and CTRS	Y	Yes	TOC in CARS
Phase 2	E1_02	SR and CTRS	Y	Yes	TOC in CARS

8.2. Statistical considerations for interim analyses

Not applicable.

9. CHANGES FROM PLANNED ANALYSES

Planned interim analyses will not be performed; eCRF and lab data will be analyzed at the same time, first for phase 1 and then for phase 2, considering that sera results release will 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	ACWY-Liq24	Subjects who received MenACWY Liquid aged 24 months
2	ACWY_1	Subjects who received Licensed MenACWY
3	ACWY-Liq30	Subjects who received MenACWY Liquid aged 30 months
4	ACWY_2	Subjects who received Licensed MenACWY

The following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	>=10 to <18 YOA	10 to 17 years old subjects
2	>=18 to <=40 YOA	18 to 40 years old subjects

10.1. 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. Br J Cancer 1978; 37: 849-857*" [White, 1978] and it is described below:

Notations

- K=1 input value [Center] to be used for minimization, each with l variants.
- Randomization ratio 1:1 within Age stratum and a_1, a2 with 1=ACWY_Liq24, 2=ACWY_1 within Phase 1, and 1=ACWY_Liq30, 2=ACWY_2 within Phase 2.

Determinism is 90% and block size is 4.

Algorithm

For a new subject with input value variants $s_1 \ldots s_K$

Step 1: Minimization computation

Step 1.1: Initialize Problem flag to 0

For each input value variant s_k, compute the number of subjects already enrolled in each treatment group.

Let b_{ik} the number for treatment i & input value variant s_k: b_{ik} is the total number of subjects already randomized (excluding subjects cancelled/withdrawn prior dose 1) in treatment i and with variant s_k.

Step 1.2: For each treatment i: compute $A_i = 1/a_i * sum_k(b_{ik})$

Step 2: determine whether the algorithm is random or deterministic:

Generate R, a random number within [0-1], uniform distribution

Step 3: check determinism

If R < 0.9, go to step 4 (determinism) else go to step 5 (random)

Step 4: determinism

Step 4.1: Identify all treatments with the lowest value A_i

Step 4.2: Select randomly one of the treatments identified in step 4.1, let it be T.

Go to step 6, if no more treatment then randomization failed

Step 5: randomization

Select randomly one of the treatments, let it be T.

Go to step 6, if no more treatment then randomization failed.

Step 6: treatment allocation

Assign one of the treatment nr. related to treatment T in the subject's center.

If no treatment nr. related to treatment T is available in the subject's center, then go & repeat step 4 (determinism) or 5 (random) while dropping treatment T (set problem flag=1).

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.

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

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

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 analysed 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 summary table 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 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 related or unknown/ missing.

Pre-study, 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 + 29 days (i.e. medication start date > last study vaccination date + 29 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.

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Table 4 Safety Sets

PD code	*PD Description*	*Study Objective/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 5 Immunogenicity Sets

PD code	**PD Description**	**Study Objective/ Period**	***FAS Day 29***	***PP Day 29***
	Exclusion code		***FAS29FL***	***PPS29FL***
1030	**Study vaccine not administered AT ALL**	Day 1 – Day 181	*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 for any of the serogroups***	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; 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-069 [V59_78]	Safety and immunogenicity in healthy adolescents and young adults 10 to 40 years of age

TOC V16 will be used.

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase 2b, randomized, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of different formulations of GSK Biologicals' Meningococcal ACWY conjugate vaccine (GSK3536820A and *Menveo*) administered to healthy adolescents and young adults 10 to 40 years of age.
eTrack study number and Abbreviated Title	207467 (MENACWY CONJ-069 [V59_78])
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 13 August 2018
Co-ordinating author:	PPD (Statistician)
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 (Lead 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 (Lead Scientific Writer)

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

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LIST OF ABBREVIATIONS

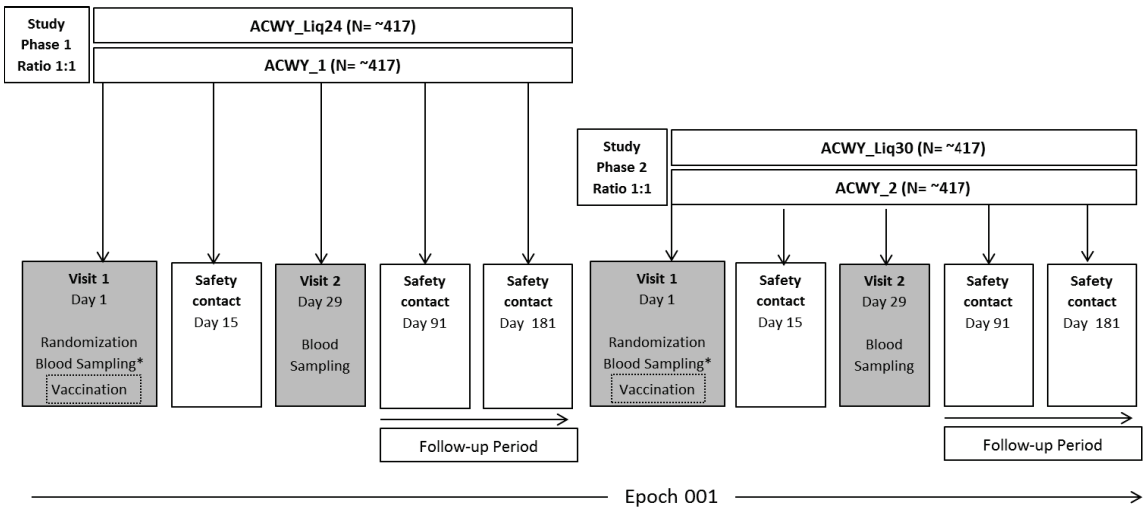
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BSP	BioStatistics and Statistical Programming
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
EoS	End of Study
ES	Exposed Set
FAS	Full Analysis Set
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
GSKDRUG	GlaxoSmithKline Drug Dictionary
hSBA	Human Serum Bactericidal Assay
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantitation
LOD	Lower Limit of Detection
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
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
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
13-AUG-2018	Final Version	Protocol Amendment 2 Final: 15-MAR-2018

2. STUDY DESIGN

Figure 1 Study design overview



*Blood sample collection from Visit 1 will be performed before vaccine administration

- Experimental design: Phase IIB, observer-blind, randomized, controlled, multi-centric study with two parallel groups per phase, in a two phases staggered design.
- Duration of the study: The duration of this study is approximately 6 months per subject.
  - 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) of Study Phase 2* if it occurs after LSLV.

  * In this case EoS must be achieved no later than 8 months after LSLV.

- Study groups:
  - **ACWY_Liq24** (Study Phase 1): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 24 months at 2-8°C;
  - **ACWY_1** (Study Phase 1): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (*Menveo*), not aged;
  - **ACWY_Liq30** (Study Phase 2): approximately 417 healthy subjects receiving investigational MenACWY liquid vaccine (GSK3536820A) aged for approximately 30 months at 2-8°C;
  - **ACWY_2** (Study Phase 2): approximately 417 healthy subjects receiving currently licensed GSK' MenACWY vaccine (*Menveo*), not aged.

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
ACWY_Liq24*	417	10 years – 40 years	x
ACWY_1	417	10 years – 40 years	x
ACWY_Liq30**	417	10 years – 40 years	x
ACWY_2	417	10 years – 40 years	x

* ACWY_Liq24: vaccine lot aged for approximately 24 months.
** ACWY_Liq30: vaccine lot aged for approximately 30 months.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/product name	Study Groups			
		ACWY_Liq24	ACWY_1	ACWY_Liq30	ACWY_2
MenACWY Liquid	MenACWY Liquid	x		x	
Licensed MenACWY (*Menveo**)	MenA lyo		x		x
	MenCWY liquid				

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

- Control: active control.
- Vaccination schedule: All subjects will receive a single dose of study vaccine at Visit 1 (Day 1).
- Treatment allocation: Randomization will be performed at Visit 1 (Day 1) using a central randomization system on the internet (SBIR), with stratification to include 40% of subjects from ≥10 to <18 YoA and 60% from ≥18 to ≤40 YoA.
- Blinding: observer-blind for each of the two phases of the study.

- Sampling schedule: Blood sample of approximately 20 ml will be collected from each subject at Visit 1 (Day 1; pre-vaccination) and at 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 using a subject Diary (electronic Diary [eDiary]).

3. OBJECTIVES

3.1. Primary objectives

- To demonstrate non-inferiority of the investigational MenACWY liquid product aged for approximately 24 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  Criterion:

  Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 24 months and the licensed MenACWY vaccine is greater than 0.5.

- To demonstrate non-inferiority of the investigational MenACWY liquid vaccine aged for approximately 30 months to that of currently licensed MenACWY vaccine, as measured by the hSBA GMTs directed against *N. meningitidis* serogroup A at Day 29 after a single dose vaccination.

  Criterion:

  Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the ratio of hSBA GMTs against serogroup A between the MenACWY liquid vaccine aged for approximately 30 months and the licensed MenACWY vaccine is greater than 0.5.

Non-inferiority hypotheses testing will be conducted sequentially, starting from vaccine lot aged for approximately 24 months and subsequently with vaccine lot aged for approximately 30 months.

3.2. Secondary objectives

- To compare the immunogenicity of the investigational MenACWY liquid products aged for approximately 24 or 30 months 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 MenACWY liquid products aged for approximately 24 or 30 months and 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: A 4-fold rise is defined as: 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; and 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 MenACWY liquid products aged for approximately 24 or 30 months and the currently licensed MenACWY vaccine, as measured by the percentage of subjects with hSBA titer ≥8 and ≥LLOQ* directed 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 MenACWY liquid vaccine aged approximately 24 or 30 months and the currently licensed MenACWY vaccine.

4. ENDPOINTS

4.1. Primary endpoints

The following measures will be summarized:

- hSBA GMTs against *N. meningitidis* serogroup A at Day 29, for each vaccine group and between-group ratios (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

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 (between vaccine serogroups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).
- Within-group ratios of hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at Day 29 compared to Day 1, for each vaccine group.
- 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 (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2).

  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 (between vaccine groups ACWY_Liq24 and ACWY_1, and ACWY_Liq30 and ACWY_2)

  * 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) 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 (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 systemic 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) for immunogenicity

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 ≥ 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 sets 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

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 / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis

PPS are subsets of FAS and should be always defined even if the objectives do not require it.

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

- Subjects who withdrew informed consent.

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, by country and by age group (≥10 to <18 YoA and ≥18 to ≤40 YoA).

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

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 analysis 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

The code ****.X will be used to identify study withdrawal from visit X.

Code	Condition under which the code is used
2120.1	Obvious deviation from Laboratory Manual or error in the laboratory data at Visit 1
2120.2	Obvious deviation from Laboratory Manual or error in the laboratory data at Visit 2
2090.1	Subjects did not comply with blood sample schedule at Visit 1
2090.2	Subjects did not comply with blood sample schedule at Visit 2

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

Codes 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 sets.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Section 11 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, age group 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, PPS (Day 29), FAS (Day 29) and Overall Safety set, by 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 FAS 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 mean between-group differences in log-transformed titers and the corresponding 95% CIs at each of the specified timepoints. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

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 mean within-group 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 country as factors in the model.

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

The percentage of subjects with a ≥ 4-fold rise in post-vaccination hSBA titer (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. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

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. Comparisons will be evaluated between vaccine groups ACWY_Liq24 and ACWY_1, and between vaccine groups ACWY_Liq30 and ACWY_2.

* 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) with vaccine group and country as factors in the model 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.

Given the 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.
A sensitivity analysis will be performed for the primary endpoint, including the age group (≥10 to <18 YoA and ≥18 to ≤40 YoA) as additional factor in the same ANCOVA model with pre-vaccination titer (Day 1) as a covariate and vaccine group and country as factors.

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 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 measurement (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 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 (with onset from Day 1 through Day 29 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

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.

6.5.2. 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

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 3 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°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 (use of antipyretics and analgesics for treatment/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 "none" (≥ 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 (to treat or to prevent pain/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 performed on the 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 GSKDRUG dictionary.

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

7. ANALYSIS INTERPRETATION

7.1.1. Primary immunogenicity objective

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

To demonstrate non-inferiority of the investigational MenACWY liquid 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. Hierarchical hypothesis testing will be performed at overall Type I Error of 2.5% (one-sided) using non-inferiority margin of 0.5 for GMT ratios.

The two hypotheses will be tested sequentially as follows:

1. Group ACWY_Liq24 versus Group ACWY_1

Null hypothesis (inferiority): $\mu_{ACWY\_Liq24} - \mu_{ACWY\_1} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{ACWY\_Liq24} - \mu_{ACWY\_1} > \log_{10}(0.5)$

Where: 0.5 is the non-inferiority margin for the ratio of GMTs between Group ACWY_Liq24 and Group ACWY_1; $\mu_{ACWY_Liq24}$and μ_{ACWY_1} are the population means of the logarithmically (base of 10) transformed titers for serogroup A in Group ACWY_Liq24 and Group ACWY_1, 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 and proceed to test the next hypothesis for Group ACWY_Liq30 versus Group ACWY_2. Otherwise, further hypothesis testing is not conducted.

2. Group ACWY_Liq30 versus Group ACWY_2

Null hypothesis (inferiority): $\mu_{ACWY\_Liq30} - \mu_{ACWY\_2} \leq \log_{10}(0.5)$ *versus*

Alternative hypothesis (non-inferiority): $\mu_{ACWY\_Liq30} - \mu_{ACWY\_2} > \log_{10}(0.5)$

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.

7.1.2. 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 this 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 availability of the Visit 2 (Day 29) immunogenicity and safety data for both the MenACWY liquid aged for approximately 24 months (ACWY_Liq24) and the *Menveo* arm (ACWY_1). This interim analysis might be reported in an interim clinical study report (CSR) for regulatory purposes.
- The analyses of safety data for the ACWY_Liq24 and ACWY_1 arms 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. This will be done together with the analysis performed on the immunogenicity and safety data for both the MenACWY liquid aged for approximately 30 months (ACWY_Liq30) and the *Menveo* arm (ACWY_2)). A final integrated CSR including the interim and the final analyses will be written at this point in time 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 25-MAY-2018
Final analysis	E1_02	SR and CTRS	Y	Yes	All tables from TFL dated 25-MAY-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 for the MenACWY liquid aged for approximately 24 months (ACWY_Liq24) and ACWY_1. This means that the interim analysis will only be performed on Phase 1 data.

The interim analysis will be performed by the BioStatistics and Statistical Programming (BSP) department. The interim analysis 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 the summary tables.

9. CHANGES FROM PLANNED ANALYSES

Not applicable

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	ACWY-Liq24	Subjects who received MenACWY Liquid aged 24 months
2	ACWY_1	Subjects who received Licensed MenACWY
3	ACWY-Liq30	Subjects who received MenACWY Liquid aged 30 months
4	ACWY_2	Subjects who received Licensed MenACWY

The following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	>=10 to <18 YOA	10 to 17 years old subjects
2	>=18 to <=40 YOA	18 to 40 years old subjects

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.

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

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

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 analysed 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 summary table 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 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 + 29 days (i.e. medication start date > last study vaccination date + 29 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.

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Table 4 Safety Sets

PD code	***PD Description***	***Study Objective/ 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 5 Immunogenicity Sets

PD code	PD Description	Study Objective/ Period	*FAS Day 29*	*PP Day 29*
	Exclusion code		***FAS29FL***	***PPS29FL***
1030	**Study vaccine not administered AT ALL**	Day 1 – Day 181	*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 for any of the serogroups***	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; 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-069 [V59_78]	Safety and immunogenicity in healthy adolescents and young adults 10 to 40 years of age