GlaxoSmithKline Biologicals

208205 MENABCWY-016 (V102_19)

A Phase II, Randomized, Open-label, Multicenter Study to Assess the Immunogenicity and Safety of GSK Meningococcal MenABCWY Vaccine, and of GSK Meningococcal Group B and MenACWY Conjugate Vaccines Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone in Healthy Subjects 10 to 25 Years of Age

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Statistical Analysis Plan

Final Version *1.0*

Prepared by: PPD

PPD
Fleming House, Phoenix Crescent
Strathclyde Business Park,
Bellshill, ML4 3NJ

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List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
BMI	Body mass index
CI	Confidence interval
CSR	Clinical Study Report
eCRF	Electronic case report form
FASx	Full Analysis Set (x = 1, 2, 3, 4)
GMR	Geometric mean ratio
GMT	Geometric mean titer
GSD	Geometric standard deviation
GSK	GlaxoSmithKline
GSKDrug	GSK Drug Dictionary
hSBA	Serum bactericidal assay using human complement
IM	Intramuscular(ly)
IMD	Invasive meningococcal disease
LAR	Legally Acceptable Representative
LLOQ	Lower limit of quantitation
LOD	Limit of detection
MAR	Missing at random
MATEX	MATerial Excellence
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculated
pDiary	Paper diary
PPSx	Per Protocol Set x (x = 1, 2, 3, 4)
SAE	Serious adverse event
SBIR	Source DataBase for Internet Randomization
SD	Standard deviation
SE	Standard error

1 Introduction

Invasive meningococcal disease (IMD) occurs when, following an average incubation period of 4 days (range: 2 to 10 days), the normally asymptomatically carried encapsulated gram-negative bacterium *N. meningitidis* enters the bloodstream and multiplies, potentially causing sepsis. If the bacteria cross the blood-brain barrier, meningitis occurs. Sepsis and meningitis caused by *N. meningitidis* are serious diseases that can be fatal or leave permanent sequelae. In European Union/European Economic Area countries, despite the availability of advanced medical treatment and effective antibiotics, case-fatality rates are high at approximately 7% to 15%, with most cases caused by serogroup B [ECDC, 2016]. Up to one fifth of survivors suffer long-term sequelae, including mental retardation, hearing loss, and loss of limb use [ECDC, 2016].

GlaxoSmithKline (GSK) Biologicals is developing a combination vaccine intended for primary immunization against *N. meningitidis* serogroups A, B, C, W-135, and Y (MenABCWY vaccine). The availability of a meningococcal vaccine based on the combination of antigens in 2 separate vaccines against serogroups ACWY (*Menveo*) and B (*Bexsero*) in a single vaccine/administration would reduce the number of injections and allow greater flexibility in dose administration schedules, and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W-135, and Y worldwide.

MenACWY is a meningococcal oligosaccharide conjugate vaccine licensed for active immunization to prevent IMD caused by *N. meningitidis* serogroups A, C, W-135, and Y. The rMenB+OMV NZ vaccine provides active immunization to prevent IMD caused by *N. meningitidis* serogroup B. The investigational MenABCWY combination vaccine is based upon the 2 aforementioned and well established GSK Biologicals' vaccines, MenACWY and rMenB+OMV NZ.

In a recent Phase IIb study MenABCWY-011 (V102_15), non-inferiority in terms of geometric mean titers (GMTs) could not be shown for 2 doses of MenABCWY versus 2 doses of rMenB+OMV NZ, given 2 months apart. Across several other studies of the MenABCWY program, immune responses against serogroup B antigens were also lower than immune responses assessed when rMenB+OMV NZ was administered alone. One possible reason that has been theorized is biological immune interference, possibly due to immunological stress to the lymph nodes in the arm where the combination vaccine is administered. The purpose of the current study is to evaluate whether there is immune interference when MenABCWY (consisting of MenACWY lyophilized component and rMenB+OMV NZ liquid component) is administered to healthy adolescents and adults following a 2-dose vaccination schedule with MenABCWY administered 2 months apart.

2 Objectives

2.1 Primary Objective

To assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY at 1 month after the last vaccination.

2.2 Secondary Objectives

Immunogenicity Objective

To assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms at 1 month after the first vaccination.

Safety Objective

To assess the safety and tolerability of 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY.

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a Phase II, randomized, open-label, controlled, multi-centric study with 5 parallel study groups. The enrollment will be performed to ensure equal distribution of the population across two age strata of 10 to 17 years and 18 to 25 years in each study group. Within each stratum the randomization algorithm will use a minimization procedure accounting for center. Approximately 500 subjects will be randomly assigned at a 1:1:1:1:1 ratio to one of five study groups:

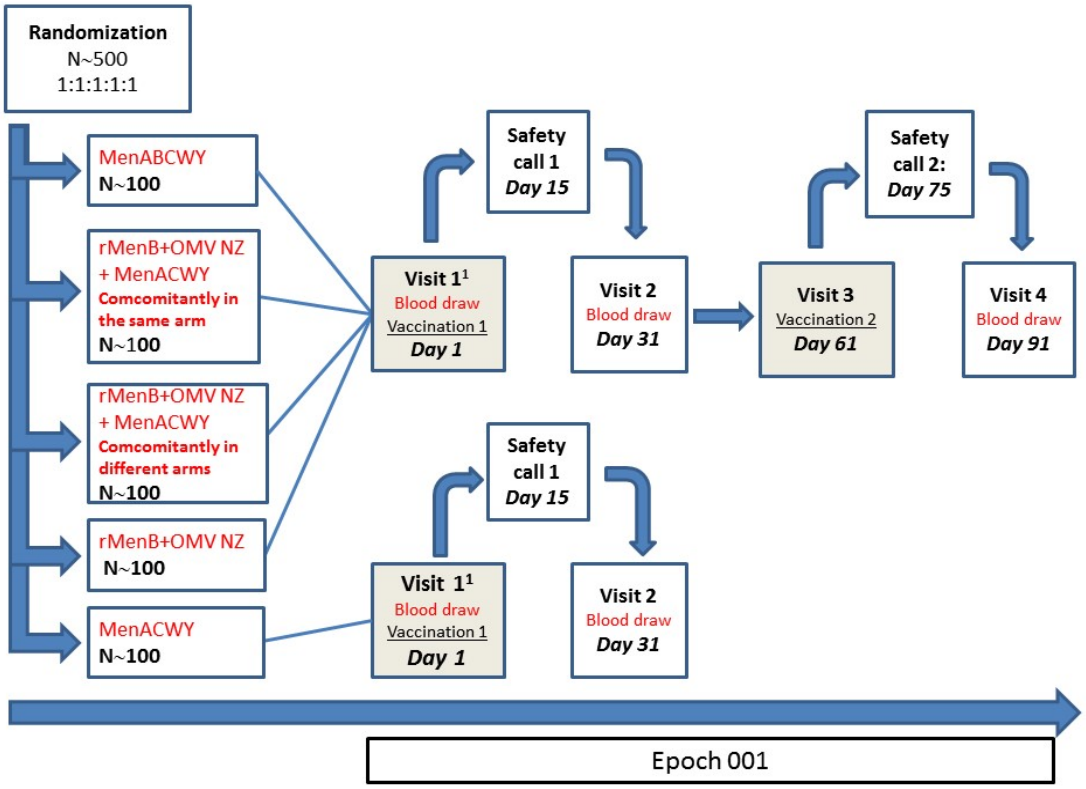
1. MenABCWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 intramuscular (IM) dose of MenABCWY twice, 2 months apart.
2. rMenBOMV+ACWY_S: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in the same arm (approximately 2.5 cm apart) twice, 2 months apart.
3. rMenBOMV+ACWY_D: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in 2 different arms twice, 2 months apart.

4. rMenBOMV: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 IM dose of rMenB+OMV NZ twice, 2 months apart.
5. MenACWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) will receive 1 IM dose of MenACWY once.

Details of the injection site location(s) can be found in Table 9.

The study design diagram is provided in Figure 1.

Figure 1 Study Design



The duration of the study is up to 91 days with subjects attending 4 visits, 30 days apart, starting at Visit 1 (Day 1) and ending at Visit 4 (Day 91). Whenever possible, the investigator should arrange study visits within the intervals described in Table 1. Visits that occur outside of the intervals will be categorized as significant protocol deviations leading to the exclusion of a subject from one of the Per Protocol sets (PPSx).

A detailed list of study procedures can be found in Section 11.2.

The signed/witnessed/thumb printed informed consent of the subject/subject's parent(s)/legally acceptable representative(s) (LARs) must be obtained before study participation. The signed informed assent of the subject below the age of consent (i.e. minor) should be obtained in addition to the signed informed consent by his/her parent(s)/LAR(s) according to local rules and regulations.

On Visit 1 (Day 1) or up to 5 days before Visit 1 (where allowed according to Table 1) informed consent will be obtained and pre-vaccination procedures will be carried out. Upon satisfactory completion of pre-vaccination procedures, subjects will be allocated a study group and treatment number and will have blood samples drawn before receiving the first dose of study vaccine(s).

Subjects will be observed closely for at least 30 minutes following the administration of the vaccine(s), with appropriate medical treatment readily available in case of anaphylaxis. Solicited adverse events (AEs) will be recorded during this 30 minute period (see Section 9.1.1 for details of solicited AEs).

Subjects will have a second dose of study vaccine(s) administered at Visit 3 (with the exception of the MenACWY group who only receive a single dose at Visit 1) following satisfactory completion of pre-vaccination procedures. Subjects will have blood drawn at Visit 1, Visit 2 and Visit 4 (with the exception of the MenACWY group who will only have blood drawn at Visit 1 and Visit 2) to test for immune response within the serogroups.

Unsolicited AEs will be recorded for 30 days following administration of study vaccine. AEs will be recorded starting from informed consent date if a separate visit occurs before Visit 1 (maximum 5 days before first dose of study vaccine). Serious adverse events (SAEs), medically attended AEs, AEs/SAEs leading to withdrawal, SAEs related to study participation or concurrent GSK medication/vaccines and adverse events of special interest (AESIs) will be recorded from the date of informed consent through Visit 4 (MenACWY group will have AEs recorded through Visit 2). Subjects will receive a safety follow-up call 14 days (or within 11 days - 17 days) after each visit where study vaccine is administered. Solicited AEs will be recorded in subject diaries by the subject/subject's parent(s)/LAR(s) for 7 days after the vaccine is administered (including the day on which the vaccine is administered).

Table 1 Visit Intervals

Interval	Optimal length of interval	Allowed interval (Min – Max)[1]
Visit 1 (Day 1) → Safety call 1 (Day 15)	14 days	11 days – 17 days (Days 12 – 18)
Visit 1 (Day 1) → Visit 2 (Day 31)	30 days	23 days – 40 days (Days 24 – 41)
Visit 1 (Day 1) → Visit 3 (Day 61)	60 days	53 days – 70 days (Days 54 – 71)
Visit 3 (Day 61) → Safety call 2 (Day 75)	14 days	11 days – 17 days (Days 72 – 78)

Visit 3 (Day 61) → Visit 4 (Day 91)	30 days	23 days – 40 days (Days 84 – 101)

[1]Safety call time intervals will not be used for the assessment of protocol deviations. The Study Day ranges shown in the table are based on optimal intervals; the actual Study Day ranges for Safety Call 2 and Visit 4 will be based on when Visit 3 occurs.

3.2 Study Endpoints

3.2.1 Primary Endpoints

Immune responses against *N. meningitidis* serogroup B* test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by hSBA, 1 month after the last vaccination in all study groups

- hSBA GMTs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA GMTs against all of *N. meningitidis* serogroup B test strains (pooled)
- Percentage of subjects with hSBA titers ≥ the lower limit of quantitation (LLOQ) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- Percentage of subjects with a 4-fold increase in hSBA titers against *N. meningitidis* serogroups B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA geometric mean ratios (GMRs) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after the last vaccination against baseline (Day 1)

*Serogroup B strains that will be tested are M14459 (factor H binding protein; fHbp), 96217 (Neisserial adhesin A; NadA), NZ98/254 (PorA), and M07-0241084 (Neisseria heparin binding antigen; NHBA) and will be pooled to estimate the effect of immune interference due to stress to lymph nodes.

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 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 4 times the LLOQ;

c) for individuals whose pre-vaccination titers are ≥ the LLOQ, the post-vaccination titers must be at least 4 times the pre-vaccination titer.

The ratios of GMTs between study groups will be analyzed to evaluate effect of treatment as described below:

a. Immune interference due to stress to lymph nodes (lymph-node effect) in rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D study groups, on the pooled B strains, and individually by serogroup A, C, W-135, Y, and B test strains.
b. Other unknown interference in the MenABCWY versus rMenBOMV+ACWY_S study groups, by serogroup A, C, W-135, Y, and B test strains.
c. The difference in immune response compared to control groups in rMenBOMV+ACWY_S versus rMenBOMV and MenACWY, rMenBOMV+ACWY_D versus rMenBOMV and MenACWY, and MenABCWY versus rMenBOMV and MenACWY study groups, by serogroup A, C, W-135, Y, and B test strains.

3.2.2 Secondary Endpoints

Immunogenicity Endpoints

Immune responses against *N. meningitidis* serogroup B* test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by hSBA, 1 month after the first vaccination in all groups (except for subjects in the MenACWY group)

- hSBA GMTs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA GMTs against all of *N. meningitidis* serogroup B test strains (pooled)
- Percentage of subjects with hSBA titers ≥ the LLOQ against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- Percentage of subjects with a 4-fold increase in hSBA titers against *N. meningitidis* serogroups B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA GMRs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after the first vaccination against baseline (Day 1)

*Serogroup B tests strains that will be tested are M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA), and M07-0241084 (NHBA).

Note: a 4-fold rise is defined in the same way as described for the primary endpoints in Section 3.2.1.

The ratios of GMTs between study groups will be analyzed to evaluate effect of treatment as described below:

a. Immune interference due to stress to lymph nodes (lymph-node effect) in rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D study groups, on the pooled B strains, and individually by serogroup A, C, W-135, Y, and B test strains.
b. Other unknown interference in MenABCWY versus rMenBOMV+ACWY_S study groups, by serogroup A, C, W-135, Y, and B test strains.
c. The difference in immune response compared to control groups in rMenBOMV+ACWY_S versus rMenBOMV, rMenBOMV+ACWY_D versus rMenBOMV, and MenABCWY versus rMenBOMV study groups, by serogroup B test strains.

<u>Safety Endpoints</u>

- Solicited local and systemic AEs in all study groups
  - Occurrence of solicited local and systemic AEs during the 7 days (including the day of vaccination) after each vaccination (Day 1 to Day 7 and Day 61 to Day 67, Day 1 to Day 7 only for subjects in the MenACWY group)

- Unsolicited AEs in all study groups
  - Occurrence of unsolicited AEs during the 30 days (including the day of vaccination) after each vaccination (Day 1 to Day 31 and Day 61 to Day 91, Day 1 to Day 31 only for subjects in the MenACWY group)
- SAEs, medically attended AEs, AEs leading to withdrawal, and AESIs, in all study groups from informed consent signature to Visit 4 (Day 91)

4 General Statistical Considerations

Treatments will be labelled on all outputs as described in Table 2.

Table 2 Treatment Labels

Treatment Number	Treatment Label
P P	MenABCWY
P P	rMenBOMV+ACWY_S[1]
P P	rMenBOMV+ACWY_D[1]
P P	rMenBOMV
P P	MenACWY

[1]S = same arm approximately 2.5cm apart, D= different arms

Categorical data will be described using the subject count and percentage in each category. A row denoted 'Missing' will be displayed to account for missing values categorical summaries. The 'Missing' row will only be displayed if at least one study group has a non-zero count for this category. Note percentages will not be displayed in the 'Missing' row, to draw attention to the percentages for the non-missing categories. Unless specified otherwise, percentages will be based on the number of subjects in each study group within the analysis population. Percentages will not be displayed if the count for a study group is zero, in order to draw attention to the percentages for non-zero counts. Percentages will be displayed using one decimal place.

Continuous data will be described using descriptive statistics (i.e. n, mean, standard deviation, minimum and maximum). For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean will be displayed to one level of precision greater than the data collected. Standard deviation/standard error will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001" If a p-value is greater than 0.999 it will be reported as ">0.999".

If statistical analysis cannot be performed for a particular serogroup or study group, then these should be displayed as "NC." (not calculated). Confidence intervals that cannot be calculated should be displayed as "(NC.)".

Data will be displayed in all listings sorted by study group. Subjects will be identified in the listings by the subject identification number.

Serogroups should be displayed in the order in Table 3. If the combined B serogroups are to be presented in a table or listing, this group should be displayed last.

Table 3 Serogroup Display Order

Serogroup (strain)	Display Order
Serogroup B (M14459)	1
Serogroup B (M07-0241084)	2
Serogroup B (96217)	3
Serogroup B (NZ98/254)	4
Serogroup C	5
Serogroup Y	6
Serogroup W-135	7
Serogroup A	8

Baseline will be defined as the value recorded at Visit 1. The study day will be calculated as assessment date - first dose date of study vaccine + 1 if the study date is on or after first dose date of study vaccine, or assessment date – first dose date of study vaccine if the study date is prior to the first dose date of study vaccine.

Throughout the study, logarithmic transformations and anti-logarithms will use base 10.

Statistical analysis will be performed using SAS® Version 9.3 or higher. Standardized and validated SAS macros from PPD will be used to set up table, listing, figure (TLF) formats (headers/footers and tabulation format) and tabulate the summaries. All tables and listings will be independently validated using double programming; datasets behind the figures will be independently validated using double programming and figure outputs will be independently validated manually.

4.1 Sample Size

Sample size calculation was performed using PASS 12 and SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Values used in sample size calculation are based on previous study MenABCWY-011 (V102_15). Because of the consistent decrease in GMT ratios in the MenABCWY group in comparison to the rMenBOMV group across the 4 serogroups in this previous study, the presence of the lymph-node effect will be tested globally on all the serogroups together.

The sample size is for exploratory statistical analysis purposes only. There are no formal confirmatory hypotheses to be tested. The text in this section describes what can be observed with the current sample size.

The potential immune interference due to immunological stress to lymph nodes is assumed to result in decreases to all of the 4 B test strains but to various extents. The sample size calculation shows that with a power range of 80% to 90%, a global lymph-node effect is detectable when the GMT ratio is between 64% (approximately -0.19 on $\log_{10}$ scale) and 74% (-0.13) pooling 4 variants of B test strains together and using a 1-sided false-positive error rate of 10%.

Assuming a rare event occurring at the rate of 1 out of 100, a sample size of 500 subjects in the study will have a probability of 99.3% to detect a rare AE.

A total of approximately 500 subjects (approximately 100 subjects in each group) are planned for enrollment into the study.

4.2 Randomization, Stratification, and Blinding

Randomization will be performed within 5 days prior to or at Visit 1 (Day 1). The randomization list will be generated using MATerial Excellence (MATEX). Central randomization will be performed using the Source DataBase for Internet Randomization (SBIR) system. Within each age stratum (10 to 17 years and 18 to 25 years) the randomization algorithm will use a minimization procedure accounting for center.

This is an open-label study. Only the laboratory in charge of the laboratory testing will be blinded to the treatment, subject, and visit number, and codes will be used to link the subject, visit, and study (without any link to the treatment attributed to the subject) to each sample.

4.3 Data Handling

Analysis Visit Names for Immunogenicity Analysis

Study visits will be derived as in Table 1. Analysis Visit names (AVISIT) will be used within the Immunogenicity Analysis. The primary endpoints are based on titer results 1 month after last vaccination so Visit 4 results are used for all study groups with the exception that the Visit 2 results for the MenACWY group will be used for the primary endpoints. The secondary endpoints are based on hSBA titer results 1 month after first vaccination so the MenACWY study group is excluded from the secondary endpoint analyses, since this group has only one visit where vaccine is administered.

Table 4 Analysis Visit Names

Visit Name	AVISIT	Study Group
Visit 1 Day 1	BASELINE	All study groups
Visit 2 Day 31	AVISIT 4	MenACWY

Visit 2 Day 31	AVISIT 2	All study groups except MenACWY
Safety Call D15	SAFETY CALL 1	All study groups
Visit 3 Day 61	AVISIT 3	All study groups except MenACWY
Visit 4 Day 91	AVISIT 4	All study groups except MenACWY
Safety Call D75	SAFETY CALL 2	All study groups except MenACWY

Titer Results

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Summaries and analyses for the pooled B serogroup strains will be performed using all available non-missing titer results. Subjects who have at least one non-missing titer result from the four possible serogroup B strains at a single visit will be included in the summaries and analyses for the pooled serogroup B strains.

Titer results recorded as below the LOD will be imputed with a numeric value of half the LOD for summaries and analyses and will be listed as reported in the raw data. For example, if an assay records a LOD of 80 and a sample is reported to have "< 80" as the titer level, a value of 40 will be used for the statistical summaries and analyses. Titer results recorded as "1:x" (where x is the dilution factor) will be assigned a numeric value of x. Titer results recorded as ">1:x" will be assigned a numeric value of x.

LOD and LLOQ values will be defined in the Clinical Study Report (CSR).

Missing Data

For safety analyses, subjects who missed reporting symptoms (solicited or unsolicited) or concomitant medications will be analyzed to determine the missing mechanism. For the analysis of solicited symptoms, implausible measurements will not be replaced but they will be excluded from the analyses. Missing values will not be imputed for solicited/unsolicited AEs or concomitant medications.

In order to minimize the effect of missing data, the study period will be divided into time intervals for the safety analyses. For unsolicited AEs, the study period will be divided into the following intervals: all unsolicited AEs reported from day 1 to day 31 after vaccination (day of vaccination = day 1, Visit 1 and Visit 3 will be assessed separately and combined), medically attended AEs reported during the entire study period, AEs leading to premature withdrawal from the study during the entire study period, SAEs reported during the entire study period and AESI reported during the study period for the Unsolicited Safety Set.

Concomitant medications will be assessed for the entire study period for the Overall Safety Set.

Solicited AE data will be analyzed by the following intervals: 30 minutes post-vaccination on day of vaccination, 1 – 3 days post-vaccination (including the day of vaccination as day 1, excluding 30 minutes post-vaccination), 4 days – 7 days post-vaccination, and 1 day - 7 days (including the day of vaccination as day 1, excluding 30 minutes post-vaccination). Intervals will be assessed for Visit 1 and Visit 3, separately and combined, for the Solicited Safety Set. Solicited local AEs will be considered separately by vaccine for study groups where two vaccinations are administered at each visit, and also separately by location

A subject will be classified as having missing data within the specified intervals as described below:

- Solicited AEs
    - Temperature will be regarded as missing if "Temperature taken" = "No" at every time point within the interval (on Post-vaccination Body Temperature eCRF page).
    - Pain will be regarded as missing if no intensity values are recorded for Vaccine A and Vaccine B separately at every time point within the interval (on Vaccine A/Vaccine B Solicited Local Adverse Event eCRF pages). An intensity value of 'None' is a valid value and will not be considered a missing value.
    - Erythema, swelling and induration will be regarded as missing if no measurements in mm are recorded for Vaccine A and Vaccine B separately at every time point within the interval (on Vaccine A/Vaccine B Solicited Local Adverse Event eCRF pages).
    - Nausea, myalgia, arthralgia, headache and fatigue will be regarded as missing if no intensity values are recorded at every time point within the interval (on Solicited General Adverse Events eCRF page). An intensity value of 'None' is a valid value and will not be considered a missing value.
- Unsolicited AEs
    - Non serious AEs will be regarded as missing if no AEs are recorded during the interval and there is no response to "Did the subject experience any non-serious adverse events during the study?" (Non Serious Adverse Event YN eCRF page).
        - Medically attended AEs will be regarded as missing if, in addition to the missing criteria for non-serious AEs, there is no response to "Medically attended visit" (Non Serious Adverse Events eCRF page).

        - AEs leading to withdrawal from the study will be regarded as missing if, in addition to the missing criteria for non-serious AEs, there is no response to "Did the subject withdraw from the study as a result of AE?" (Non Serious Adverse Events eCRF page).
    - Serious AEs will be regarded as missing if no SAEs are recorded during the interval and there is no response to "Did the subject experience a serious adverse event or a non-serious AESI during the study?" (Serious/Expedited Event YN eCRF page), or "Did the subject experience a serious adverse event or a non-serious AESI during the study?" = "Yes" and there is no response to "Serious" (Serious/Expedited Event eCRF page).
    - AESI will be regarded as missing if there is no response to "Did the subject experience any arthritis/arthralgia (joint pain) events during the study?" (Arthritis/Arthralgia (Joint Pain) Events YN eCRF page).
- Concomitant medications will be regarded as missing if no concomitant medications are recorded on the Concomitant Medications eCRF page, and there is no response to "Were any medications taken?" on the Concomitant Medications YN eCRF page.

The following algorithm will be applied to each interval:

1. If less than 20% of subjects are without any solicited AE/unsolicited AE/concomitant medication data (i.e. no solicited AE/unsolicited AE/concomitant medication data have been captured) for the respective data/visit/time interval, then no assumptions will be made about the missing mechanism.
2. If 20% or more of subjects are without any solicited AE/unsolicited AE/concomitant medication data, the missing mechanism will be analyzed using a newly created variable indicating whether a subject has any respective data values or not.
    a. If the percentage of missing subjects does not vary significantly between study groups (Fisher's Exact $p \geq 0.05$) then 'missing completely at random' (MCAR) is assumed.
    b. If the percentage of missing subjects varies significantly between study groups (Fisher's Exact $p < 0.05$) then 'missing at random' (MAR) is assumed, i.e., the missing mechanism is conditional on the vaccine group. The denominator used to calculate percentages will be reduced by the number of subjects with missing values to reduce bias through inflated 'no AE' counts.

The number and percentage of subjects with no data recorded for each time interval specified for solicited AEs, unsolicited AEs and concomitant medications will be presented in a table for the All Enrolled Set, along with the p-value for Fisher's Exact test.

Implausible Values for Vital Signs and Solicited Adverse Events
The following numeric values will be considered implausible and will be excluded from summaries:

- Erythema: values less than 0 mm or equal to or greater than 500 mm
- Induration: values less than 0 mm or equal to or greater than 900 mm
- Temperature: values less than or equal to 33.0°C or equal to or greater than 42.0°C.

4.4 Analysis Sets

4.4.1 All Enrolled Set

All subjects who signed an informed consent, underwent screening procedures, and have a subject number assigned.

4.4.2 All Exposed Set

All subjects in the All Enrolled Set who receive any study vaccination.

4.4.3 Safety Sets

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

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

- All subjects in the All Exposed Set with any solicited AE data.

Unsolicited Safety Set (unsolicited adverse events)

- All subjects in the All Exposed Set who attended at least 1 visit or had at least 1 safety call or at least 1 follow-up event (such as withdrawal from the study) after receiving any study vaccination.

Overall Safety Set

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

4.4.4 Full Analysis Sets (FASx), Immunogenicity

FASx will be defined by visit and serogroup/B strain.

Full Analysis Set 1

- All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup or B strain at Visit 4 for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group.

Full Analysis Set 2

- All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup or B strain at Visit 2 for all study groups except the MenACWY group.

Full Analysis Set 3

- All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup or B strain at Visit 4 for all study groups except the MenACWY group, or at Visit 2 for the MenACWY group and at baseline for all study groups.

Full Analysis Set 4

- All subjects in the All Exposed Set who provided evaluable serum samples and whose assay results are available for at least 1 serogroup or B strain at Visit 2 and at baseline for all study groups except the MenACWY group.

4.4.5 Per Protocol Set (PPSx), Immunogenicity

PPS1, PPS2, PPS3, and PPS4 are the corresponding subsets of FAS1, FAS2, FAS3, and FAS4, respectively, who have no significant protocol deviations leading to exclusion from PPSx.

Protocol deviations are described in Section 5.2.

5 Subject Disposition

5.1 Disposition

Subject disposition will be summarized for the All Enrolled Set and for the Overall Safety Set, for each study group and overall. The summary will include the number of subjects in each analysis set defined in Section 4.4, the number and percentage of subjects who received any study vaccination, the number and percentage of subjects who were screen failures and major reason for screen

failure, the number and percentage of subjects who completed the study and the primary reason for withdrawal from the study.

Listings will be provided for disposition data based on the All Enrolled Set.

5.2 Significant Protocol Deviations

A significant protocol deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity results of the subject and will cause a subject to be excluded from PPSx. The number and percentage of subjects with each significant protocol deviation leading to exclusion from each PPSx will be presented and a listing of all significant protocol deviations leading to exclusion from PPSx will also be presented. Significant protocol deviations leading to exclusions from PPSx will be summarized by study group and overall for the All Enrolled Set.

All protocol deviations will be identified prior to the analysis and a clinical judgment will be necessary to classify each deviation as "significant" or "non-significant". A list of key significant deviations is provided below, but not limited to:

- Subjects enrolled who did not meet entry criteria including age at enrollment
- Subjects incorrectly vaccinated
- Subjects who did not receive study vaccinations as planned in protocol
- Subjects who did not have blood draws as planned in protocol
- Subjects with a blood draw outside of allowed time window
- Subjects with a vaccination done outside of allowed time window
- Subjects who incur a condition that has the capability of altering their immune response (i.e. human immunodeficiency virus or hematological malignancies) or are confirmed to have an alteration of their initial immune status.
- Subjects who receive any of the following during the study:
    - Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.
    - Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 consecutive days in total) during the study period. Inhaled and topical steroids are allowed.

- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period of 14 days (for inactivated vaccines), 28 days (for live vaccines), or 7 days (for influenza vaccines) before or after administration of the study vaccine(s) at Visit 1 and Visit 3*.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC and according to local governmental recommendations and provided a written approval of the sponsor is obtained.
- Drug and/or alcohol abuse that, in the opinion of the investigator, will interfere with the results of the study or pose additional risk to the subject.

These key significant deviations will be assessed based on the data collected in the electronic case report forms (eCRFs). The complete list of protocol deviations considered significant for this study will be reported in the Clinical Study Report (CSR). If a subject incurs a condition that has the capability of altering their immune response, this will be recorded as an AE and identified as a significant protocol deviation by medical monitoring.

6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the All Enrolled Set, All Exposed Set, Per Protocol Set 3, Full Analysis Set 3 and Overall Safety Set, presented by study group and overall. Subject demographic and baseline characteristics will also be presented in a listing for the All Enrolled Set.

6.1 Demographics

The demographic characteristics consist of sex, race and center. The number and percentage of subjects by sex (Male, Female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other) and center, will be reported.

6.2 Baseline Characteristics

The baseline characteristics consist of age (years), age strata, baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2). Age is calculated as the number of days between the date of birth and the date of first

vaccination, converted to years. To ensure that the collection of date of birth will not jeopardize the privacy of personally identifiable information, only year of birth (YYYY) is collected on the eCRF. Date of birth will be imputed as 30JUNYYYY and Age will be calculated as (date of first vaccination – 30JUNYYYY)/365.25. BMI is calculated as (body weight in kilograms) / (height in meters)^2.

Age (years), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of subjects by age strata (10-17 years, 18-25 years), and by center and age strata will also be reported.

6.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher. The number and percentage of subjects with any medical history will be summarized overall and for each system organ class and preferred term by study group. Percentages will be calculated based on number of subjects in the All Enrolled Set by study group and overall.

Subject medical history data will also be presented in a listing.

6.4 Inclusion and Exclusion Criteria

Subjects who did not meet inclusion criteria or met exclusion criteria will be presented in a listing for the All Enrolled Set. Inclusion and exclusion criteria are listed in the protocol sections 4.2 and 4.3.

7 Treatments and Medications

7.1 Vaccination History and Concomitant Medications

All vaccinations and medications will be coded according to the GSK Drug dictionary (GSKDrug) version 1.4 or higher.

7.1.1 Vaccination History

The number and percentage of subjects with any prior vaccinations recorded on the eCRF will be summarized by study group and overall, and the number and percentage of subjects who received each vaccination will be presented. Prior vaccinations will be displayed in a listing. All summaries will be performed using the All Enrolled Set.

7.1.2 Concomitant Medications

Concomitant medications are defined as any medications/products, except vitamins and dietary supplements, administered through 30 days post-vaccination.

A concomitant vaccination is defined as a vaccination administered in the period starting 28 days before the first dose of study vaccine(s) and ending at the last study visit (Day -28 to last study visit).

The number and percentage of subjects with at least one concomitant medication/vaccination will be summarized by study group and overall and the number and percentage of subjects taking each medication/receiving each vaccination will be presented by preferred term. Concomitant medications/vaccinations will be displayed in a listing. All summaries will be performed using the Overall Safety Set. Subjects with missing concomitant medication data will be handled as described in Section 4.3.

7.2 Extent of Exposure

Extent of exposure will be based on the All Enrolled Set and will be presented by study group and overall.

7.2.1 Compliance

The number and percentage of subjects who received any study vaccination will be presented, as well as the number and percentage of subjects who received all expected vaccinations during the study and the number and percentage of subjects who withdrew from study vaccine. A subject has withdrawn from study vaccine if

- For all study groups except MenACWY:
  - Vaccination was administered at Visit 1, no vaccination was administered at Visit 3 and the subject has data recorded for at least one of the following: Safety Call D75; Visit 4 or
  - Vaccination was not administered at Visit 1 and vaccination was not administered at Visit 3 and the subject has data recorded for at least one of the following: Safety Call D75; Visit 4.
- For MenACWY study group:
  - No vaccination was administered at Visit 1and the subject has data recorded for at least one of the following: Safety Call D15; Visit 2.

In addition, the number and percentage of subjects who did not receive all vaccinations with reason (including subjects who received a partial vaccination) will be displayed by visit. The number of expected vaccinations for each study group can be found in Table 5.

Table 5 Expected Number of Vaccinations

Study Group	Expected Number of Vaccinations at Visit 1	Expected Number of Vaccinations at Visit 3*

MenABCWY	1	1
rMenBOMV + ACWY_S	2	2
rMenBOMV + ACWY_D	2	2
rMenBOMV	1	1
MenACWY	1	-

* Subjects in the MenACWY group do not receive any vaccination at Visit 3.

7.2.2 Visit Attendance

The number and percentage of subjects who attended a visit or received a safety call within the interval described in Table 1 will be presented for the following visits:

- Visit 1
- Safety Call 1
- Visit 2
- Visit 3 (excluding the MenACWY group)
- Safety Call 2 (excluding the MenACWY group)
- Visit 4 (excluding the MenACWY group)

The number and percentage of subjects who received a 3 day pDiary reminder call and a 5 day pDiary reminder call after each visit, and if the subject/legal guardian was reached, will also be included.

Listings will be provided for the All Enrolled Set to provide details of visit attendance, safety calls, blood samples and pDiary reminder calls.

8 Immunogenicity Analysis

One of the main objectives of the study is to estimate the extent of a potential immune interference, due to immunological stress to lymph nodes in the arm where the combination vaccine is administered in comparison to injections in 2 different arms of individual vaccines. The sample size defines the conditions under which the observed reduction in immune response will be attributed to a true lymph-node effect or is the consequence of natural variability. An acceptable probability of falsely detecting the lymph-node effect was set to 10% (1-sided test). The minimum probability of detecting the lymph node effect is set to 80%.

Immune response will be measured using serum bactericidal assay using human complement (hSBA) testing performed on serum samples and titer results will be

analyzed for the immunogenicity analysis. Titers below LOD will be handled as described in Section 4.3.

The primary and secondary analysis will be based on PPSx. If the difference between PPSx and FASx is greater than 10%, a second analysis based on FASx will be performed to complement the PPSx analysis i.e. an analysis can be performed for PPS3 and FAS3, and for PPS4 only.

Titer results will be listed for the All Enrolled Set and the listing will indicate subjects included in each of PPSx and FASx. The listing will also indicate subjects with hSBA titers ≥ LLOQ and subjects who experienced a 4-fold increase in hSBA titers since baseline.

For the remainder of Section 8 the Analysis Visit names defined in Table 4 will be used.

8.1 Summary and Analysis of hSBA Geometric Mean Titer

8.1.1 Primary Endpoint

Titer results are not normally distributed so summary statistics will be calculated using log-transformed titer results. The anti-logarithm of the summary statistics will be presented. Titer results will be summarized by study group, visit (Baseline, AVISIT 4) for each serogroup (A, C, W-135, Y) and the four individual serogroup B test strains. Titer results will also be summarized for the pooled serogroup B test strains. Missing titer results and results below the LOD will be handled as described in Section 4.3. Unadjusted and adjusted summaries will be calculated and will be displayed in the same output.

In addition, the distribution of antibody titers for each serogroup (A, C, W-135, Y) and the individual serogroup B test strains will be displayed using reverse cumulative distribution curves. The x-axis of the reverse cumulative distribution curves will be presented on a log scale. A reference line will be included to show LLOQ. All study groups for a single visit will be displayed on the same page, and visits will be displayed on separate pages.

Unadjusted summaries will include the number of subjects with non-missing titer results, geometric mean titer (GMT), geometric standard deviation (GSD), 80% confidence interval (CI) for GMT, minimum and maximum.

GMT will be calculated as the anti-logarithm of the mean of the log-transformed titer values i.e. anti-logarithm of $\sum(log_{10}(titer))/n$ where n is the number of subjects with non-missing titer results. GSD will be calculated as the anti-

logarithm of the standard deviation (SD) of the log-transformed data. The 80% CI for GMT will be calculated as the anti-logarithm of the endpoints of the 80% CI for the mean of the log-transformed data. The anti-logarithm is calculated as 10^x where x is the statistic of interest calculated from the log-transformed data (e.g. mean, SD, 80% CI endpoints).

Adjusted summaries will be calculated using an analysis of covariance (ANCOVA) model. The adjusted GMT, standard error (SE) and 80% CI from the ANCOVA model will be presented.

Two ANCOVA models will be fitted, ANCOVA1 and ANCOVA2. ANCOVA1 will be used to estimate adjusted summaries for individual serogroups A, C, W-135, Y and the individual serogroup B test strains. ANCOVA2 will be fitted to the serogroup B data only to obtain adjusted summaries for the pooled serogroup B test strains.

ANCOVA1 for the immunogenicity analysis will be fitted in SAS using PROC MIXED. ANCOVA2 will be fitted using PROC MIXED with a REPEATED statement to account for within subject correlation. The TYPE =UN option will be used to specify an unstructured covariance model. The unstructured model was used to estimate sample study and does not make any assumptions about the form of the covariance structure in the data. The models will be fitted as follows:

ANCOVA1

- The fixed-effect model will include age strata, study group, and center as fixed effects. The pre-vaccination (Baseline) log-transformed titer with centering at zero will be included as a continuous covariate.
- The model will be fitted to each serogroup/strain* separately.

* a categorical variable will be used to indicate if the dependent variable (response) is for serogroup A, C, W-135, Y or individual serogroup B test strain M14459, 96217, NZ98/254 or M07-0241084.

ANCOVA2

- The fixed-effect model will include age strata, study group, strain** and center as fixed effects. The pre-vaccination (Baseline) log-transformed titer with centering at zero will be included as a continuous covariate. An interaction between strain* and pre-vaccination log-transformed titer centered at zero will be included in the model.
- The model will be fitted to the serogroup B test strain data only.

** a categorical variable will be used to indicate if the dependent variable (response) is for serogroup B test strain M14459, 96217, NZ98/254 or M07-0241084.

For each study group, adjusted GMTs, SEs and 80% CI for GMT will be obtained by taking the anti-logarithm of the least squares means, the SE and the lower and upper limits of the 80% CIs of the log-transformed titers. The pre-vaccination log-transformed titer will be zero centered as follows: *log-transformed titer for each subject at Baseline – mean(log-transformed titer for all subjects at Baseline)* i.e. centering will occur after the titer results have been log transformed.

The contrasts in Table 6 will be computed at AVISIT 4 based on PPS3 to investigate possible effects on the immune response based on strains common to each study group.

No adjustment will be made for multiple comparisons.

rMenBOMV+ACWY_S will be declared statistically inferior if the 2-sided 80% CIs of the ratio of the GMT with rMenBOMV+ACWY_D as control is lower than 1 at 1 month after last vaccination. The lymph-node effect would therefore be the most probable cause for the decrease observed.

Table 6 Contrasts for GMT from ANCOVA Models - Primary

Contrast	Serogroup and Strains	Model
rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D (test for immune interference, due to immunological stress to lymph node)	A, C, W-135, Y Individual B strains Pooled B strains	ANCOVA1 ANCOVA1 ANCOVA2
MenABCWY versus rMenBOMV+ACWY_S (test for other unknown immunological interference)	A, C, W-135, Y Individual B strains	ANCOVA1 ANCOVA1
rMenBOMV+ACWY_S versus rMenBOMV	Individual B strains	ANCOVA1
rMenBOMV+ACWY_S versus MenACWY	A, C, W-135, Y	ANCOVA1
rMenBOMV+ACWY_D versus rMenBOMV	Individual B strains	ANCOVA1
rMenBOMV+ACWY_D versus MenACWY	A, C, W-135, Y	ANCOVA1
MenABCWY versus rMenBOMV	Individual B strains	ANCOVA1
MenABCWY versus MenACWY	A, C, W-135, Y	ANCOVA1

The following outputs will be produced:

- Unadjusted and adjusted summary statistics (n, GMT, GSD, 80% CI for GMT, minimum, maximum, ANCOVA results: GMT, SE, 80% CI for GMT) at Baseline and AVISIT 4, based on PPS3.
- Contrasts from Table 6.

8.1.2 Secondary Endpoint

The analyses described in Section 8.1.1 will be repeated using AVISIT 2 instead of AVISIT 4, with the exception that the contrasts defined in Table 7 will be calculated (instead of Table 6). The MenACWY study group is not included in the secondary analyses.

Table 7 Contrasts for GMT from ANCOVA Models - Secondary

Contrast	Serogroup and Strains	Model
rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D (test for immune interference, due to immunological stress to lymph node)	A, C, W-135, Y Individual B strains Pooled B strains	ANCOVA1 ANCOVA1 ANCOVA2
MenABCWY versus rMenBOMV+ACWY_S (test for other unknown immunological interference)	A, C, W-135, Y Individual B strains	ANCOVA1 ANCOVA1
rMenBOMV+ACWY_S versus rMenBOMV	Individual B strains	ANCOVA1
rMenBOMV+ACWY_D versus rMenBOMV	Individual B strains	ANCOVA1
MenABCWY versus rMenBOMV	Individual B strains	ANCOVA1

The following outputs will be produced:

- Unadjusted and adjusted summary statistics (n, GMT, GSD, 80% CI for GMT, minimum, maximum, ANCOVA results: GMT, SE, 80% CI for GMT) at Baseline and AVISIT 2 based on PPS4.
- Contrasts from Table 7.

8.2 Geometric Mean Ratios

8.2.1 Primary Endpoint

GMR will be summarized by study group at AVISIT 4 for each serogroup (A, C, W-135, Y) and the four individual serogroup B test strains. Missing titer results and results below the LOD will be handled as described in Section 4.3. Unadjusted and adjusted summaries will be calculated and presented in the same output.

GMR will be calculated as the anti-logarithm of the mean of the change from baseline of log-transformed titer values at AVISIT 4 and Baseline i.e. anti-logarithm of $\sum(log_{10}(titer_{Avisit\ 4}) - log_{10}(titer_{Baseline}))/n$ where n is the number of subjects with non-missing titer results at Baseline and AVISIT 4.

Unadjusted summaries will include the number of subjects with non-missing titer results at AVISIT 4, GMR, GSD of the difference in log-transformed titer results at AVISIT 4 and Baseline, 80% CI for GMR, minimum and maximum.

GSD will be calculated as the anti-logarithm of the SD of the change from baseline of the log-transformed data. The 80% CI for GMR will be calculated as the anti-logarithm of the endpoints of the 80%CI for the mean GMR. The anti-logarithm is calculated as 10^x where x is the statistic of interest calculated from the log-transformed data (e.g. mean, SD, 80% CI endpoints).

Adjusted summaries will be calculated using an ANCOVA model. The adjusted GMR, SE and 80% CI from the ANCOVA model will be presented. ANCOVA1 from Section 8.1.1 will be fitted to each serogroup/strain individually.

For each study group, adjusted GMRs, SEs and 80% CI for GMR will be obtained by taking the anti-logarithm of the least squares means, the SE and the lower and upper limits of the 80% CIs of the difference between log-transformed titers. The pre-vaccination log-transformed titer will be zero centered as follows: *log-transformed titer for each subject at Baseline – mean(log-transformed titer for all subjects at Baseline)* i.e. centering will occur after the titer results have been log transformed.

The contrasts in Table 6 will be computed (ANCOVA1 only) based on PPS3 to investigate possible effects on the immune response based on strains common to each study group.

No adjustment will be made for multiple comparisons.

The following results will be produced and presented in the same output containing the results from Section 8.1.1:

- Unadjusted and adjusted summary statistics (n, GMR, GSD, 80% CI for GMR, minimum, maximum, ANCOVA results: GMR, SE, 80% CI for GMT), based on PPS3.
- Contrasts from Table 6 (ANCOVA1 only).

8.2.2 Secondary Endpoint

The analyses described in Section 8.2.1 will be repeated using AVISIT 2 instead of AVISIT 4, with the exception that the contrasts defined in Table 7 will be calculated. The MenACWY study group is not included in the secondary analyses.

The following results will be produced and presented in the same output containing the results from Section 8.1.2:

- Unadjusted and adjusted summary statistics (n, GMR, GSD, 80% CI for GMR, minimum, maximum, ANCOVA results: GMR, SE, 80% CI for GMT), based on PPS4.
- Contrasts from Table 7 (ANCOVA1 only).

8.3 Summary and Analysis of Percentage of Subjects With Titers Above LLOQ

8.3.1 Primary Endpoint

This endpoint will be summarized for PPS3.

The percentage of subjects with titers above the LLOQ as well as the associated 2-sided 80% Clopper-Pearson CIs [Clopper, 1934] will be computed by study group at AVISIT 4.

In addition, differences in percentages of subjects with titers above the LLOQ and 2-sided 80% CIs between selected study groups will be calculated using the method of Miettinen and Nurminen [Miettinen, 1985]. The following differences will be calculated:

- rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D (test for immune interference, due to immunological stress to lymph node)
- MenABCWY versus rMenBOMV+ACWY_S (test for other unknown immunological interference)
- rMenBOMV+ACWY_S versus rMenBOMV
- rMenBOMV+ACWY_S versus MenACWY
- rMenBOMV+ACWY_D versus rMenBOMV
- rMenBOMV+ACWY_D versus MenACWY
- MenABCWY versus rMenBOMV
- MenABCWY versus MenACWY

No adjustments will be made for multiple comparisons.

8.3.2 Secondary Endpoint

This endpoint will be summarized for PPS4.

The percentage of subjects with titers above the LLOQ as well as the associated 2-sided 80% Clopper-Pearson CIs [Clopper, 1934] will be computed by study group at AVISIT 2. Note that the MenACWY group is not included in the secondary analysis.

In addition, differences in percentages of subjects with titers above the LLOQ and 2-sided 80% CIs between selected study groups will be calculated using the method of Miettinen and Nurminen [Miettinen, 1985]. The following differences will be calculated:

- rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D (test for immune interference, due to immunological stress to lymph node)
- MenABCWY versus rMenBOMV+ACWY_S (test for other unknown immunological interference)
- rMenBOMV+ACWY_S versus rMenBOMV
- rMenBOMV+ACWY_D versus rMenBOMV
- MenABCWY versus rMenBOMV

No adjustments will be made for multiple comparisons.

8.4 Summary and Analysis of Percentage of Subjects With a 4-fold Increase in hSBA Titer

8.4.1 Primary Endpoint

This endpoint will be summarized for PPS3.
The analysis described in Section 8.3 will be repeated for subjects with a 4-fold increase in hSBA titer at AVISIT 4 since Baseline.

A 4-fold increase is defined as:

a) for individuals whose pre-vaccination titers are < 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 4 times the LLOQ;
c) for individuals whose pre-vaccination titers are ≥ the LLOQ, the post-vaccination titers must be at least 4 times the pre-vaccination titer.

8.4.2 Secondary Endpoint

This endpoint will be summarized for PPS4.

The analysis described in Section 8.3 will be repeated for subjects with a 4-fold increase in hSBA titer at AVISIT 2 since Baseline.

A 4-fold increase is defined as:

a) for individuals whose pre-vaccination titers are < 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 4 times the LLOQ;
c) for individuals whose pre-vaccination titers are ≥ the LLOQ, the post-vaccination titers must be at least 4 times the pre-vaccination titer.

9 Safety Analysis

Adverse events summaries will be based on the Solicited Safety Set, the Unsolicited Safety Set and the Overall Safety Set as described below.

9.1 Adverse Events

Solicited AEs, unsolicited AEs, SAEs, medically attended AEs, AEs leading to withdrawal from treatment or from the study, and AEs of special interest (AESI) that occur post-vaccination will be summarized and also presented in listings. AEs occurring prior to a subject receiving any study vaccine will be listed only.

The definitions for SAEs and medically attended AEs and AESIs can be found in protocol sections 8.1.2 and 8.3.3.4 respectively. Further information about AESIs can be found in Section 9.1.3.

Incomplete onset dates and end dates for any AEs will be imputed to determine if the event occurred within the time period specified for AE summaries as described in sections 9.1.1, 9.1.2 and 9.1.3. Actual dates recorded will be presented in listings, imputed dates will not be presented. Incomplete dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study vaccine, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study vaccine month and year, and the end date (after any imputation) is on or after the first dose of study vaccine, then assume the date of the first dose of study vaccine. If the month and year are the same as the first dose of study vaccine month, and year and the end date (after any imputation) is prior to the first dose of study vaccine, then assume the end date for the onset date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is before the year of first dose of study vaccine, assume DD-JAN-YYYY/01-JAN-YYYY of the collected year. If the year is after the first dose and the same as the second

dose, assume DD-JAN-YYYY/01-JAN-YYYY. If the year is the same as the first dose of study vaccine year, and the end date (after any imputation) is on or after the first dose of study vaccine, then assume the date of the first dose of study vaccine. If the year is the same as the first dose of study vaccine, and the end date (after any imputation) is prior to the first dose of study vaccine, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month.
- DD-UKN-YYYY: Assume DD-DEC-YYYY.
- UK-UKN-YYYY: Assume 31-DEC-YYYY.

9.1.1 Solicited Adverse Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited AEs") occurring in the hours and days following a vaccination. Subjects will be assessed for reactogenicity, to be collected by the subjects/parent(s)/LAR(s) for 7 days following each vaccination (the day of vaccination and the following 6 days), using a subject diary (pDiary). Solicited AEs will be recorded in the pDiary for the periods Day 1 to Day 7 and Day 61 to Day 67, with the exception that subjects in the MenACWY group who will have solicited AEs recorded only for Day 1 to Day 7. Solicited AEs occurring within 30 minutes of vaccination on Day 1 and Day 61 will be recorded by the investigator on the eCRF and will not be included in the pDiary. The MenACWY group will only have solicited AEs recorded for Day 1 to Day 7 (including 30 minutes post-vaccination on Day 1).

Solicited local AEs

Solicited local (injection site) AEs for this study are pain, erythema, swelling, and induration. Solicited local AEs will be recorded according to the vaccine that was administered and the site of administration (e.g. upper or lower deltoid and the arm used for administration).

Solicited systemic AEs

Solicited systemic AEs for this study are fever (body temperature $\geq$ 38.0°C), nausea, myalgia, arthralgia, headache, and fatigue. The preferred location for measuring temperature in this study is the axilla.

Other solicited AEs

The use of analgesics/antipyretics (preferably paracetamol) for either prophylactic or treatment purposes will also be recorded as other solicited events in the pDiary and summarized with the solicited AEs.

Note: Any solicited AE that meets any of the following criteria will be entered into subjects' source document and also as an AE on the eCRF:

- Solicited local or systemic AE that continues beyond day 7 after vaccination.
- Solicited local or systemic AE that leads to a visit to a healthcare provider (medically attended AE).
- Solicited local or systemic AE leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (AE leading to withdrawal).
- Solicited local or systemic AE that otherwise meets the definition of an SAE.

Solicited AE's will be summarized according to the defined severity grading scales in Table 8. Body temperature will be classified as <38°C (no fever) and ≥38°C (fever), as well as by 0.5°C increments from 36.0°C up to ≥40°C.

Missing values for solicited AEs will be handled as described in Section 4.3.

Table 8 Solicited Adverse Event Intensity Grades

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities
	2	Moderate: Painful when limb is moved and interferes with every day activities
	3	Severe: Significant pain at rest. Prevents normal every day activities
Erythema at injection site Swelling at injection site Induration at injection site	0	None: <25 mm surface diameter
	1	Mild: 25-50 mm surface diameter
	2	Moderate: 51-100 mm surface diameter
	3	Severe: >100 mm surface diameter

Fever[1]		Record temperature in °C
Nausea	0	None
	1	Mild: Nausea present but not interfering with oral intake
	2	Moderate: Nausea leading to decreased oral intake
	3	Severe: Nausea leading to minimal to no oral intake
Myalgia	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity
Headache	0	None
	1	Mild: Headache present but does not interfere with activity
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	None
	1	Mild: Fatigue that does not interfere with activity
	2	Moderate: Fatigue that causes some interference with activity
	3	Severe: Fatigue that prevents daily activity

[1]The preferred route for measuring and recording temperature in this study is the axilla. When there is no other alternative, the temperature may be recorded by another route. If the temperature is taken by another route (oral, rectal, or tympanic), the route should be documented. Fever is defined as a body temperature ≥38°C.
Note: Temperature will be recorded in the evening. If additional temperature measurements are to be performed at other times of the day, the highest temperature measured will be recorded in the eCRF.

A summary table containing the number and percentage of subjects showing the occurrence of any local or systemic AE will be presented by study group and visit (Visit 1, Visit 3 and Any visit, the MenACWY group will only be included in Visit 1 and Any visit).

Subjects with solicited AEs will be counted based on actual treatment received for each study group using the Solicited Safety Set. The following categories will be included in the summary table for solicited AE:

1. Subjects who experienced any solicited AE within 7 days of vaccination
2. Subjects who experienced any systemic solicited AE within 7 days of vaccination
3. Subjects who experienced any local solicited AE within 7 days of vaccination
4. Subjects who experienced any local solicited AE on upper left deltoid within 7 days of vaccination
5. Subjects who experienced any local solicited AE on lower left deltoid within 7 days of vaccination

6. Subjects who experienced any local solicited AE on upper right deltoid within 7 days of vaccination
7. Subjects who experienced any local solicited AE on lower right deltoid within 7 days of vaccination
8. Subjects who experienced any other solicited AE within 7 days of vaccination

Categories 1 - 8 will be repeated for the following time points:

- Within 30 minutes of vaccination
- Within 1-3 days of vaccination (excluding 30 minutes post-vaccination)
- Within 4-7 days of vaccination

The number and percentage of subjects experiencing each solicited AE will be presented for each symptom maximal severity (defined in Table 8) by study group, visit (Visit 1, Visit 3 and Any visit, with the MenACWY group only included for Visit 1 and Any visit), and time point (30 minutes post vaccination, days 1 to 3 excluding 30 minutes post vaccination, days 4-7, days 1-7 excluding 30 minutes post-vaccination). Local solicited AEs will also be presented by maximal severity and site of administrate: upper or lower deltoid, left or right arm. Pain and fever will also be summarized by the use of antipyretics/analgesics for the prevention and/or treatment of pain/fever.

If a solicited AE occurs more than once for a subject within a time point, it will be counted in the summary only once, according to the maximal severity.

Solicited AEs will be listed and the use of antipyretics/analgesics will be highlighted.

9.1.2 Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using a pDiary and that was spontaneously communicated by a subjects/parent(s)/LAR(s) who has signed the informed consent or a solicited local or systemic that meets the criteria described in Section 9.1.1. Solicited AEs lasting more than 7 days after vaccination (including the day of vaccination) are also recorded as AEs.

The original verbatim terms used by investigators to identify AEs in the Adverse Events page of the eCRF will be mapped to preferred terms (PT) using MedDRA version 20.1 or higher. The AEs will then be grouped by MedDRA preferred terms according to system organ class (SOC).

Unsolicited AE summaries will be based on the Unsolicited Safety Set.

The following summaries will present the number and percentage of subjects reporting each AE and will be presented by SOC and PT for each study group, grouped by three time points: 30 days post-vaccination at any visit, 30 days post-vaccination at Visit 1 and 30 days post vaccination at Visit 3. Note that the MenACWY group will not be included in the 30 days post vaccination at Visit 3 summary):

- Any unsolicited AE
- Unsolicited AEs that are possibly or probably related to vaccine(s) - (Relationship to study treatment = Yes)
- Severity of unsolicited AE

Additional summaries will present the number and percentage of subjects reporting AEs in the following categories and will be presented by SOC and PT for each study group from Day1 through till end of study for the Overall Safety Set:

- AEs leading to withdrawal from the study
- AEs leading to withdrawal from the study vaccine
- AEs leading to a medically attended visit
- AEs leading to death
- SAEs
- SAEs that are possibly or probably related to vaccine(s)
- SAEs leading to death
- SAEs that are possibly or probably related to vaccines(s) and leading to death

Listings will be presented for Any AEs, AEs that are possibly or probably related to vaccine(s), AEs leading to withdrawal from the study, AEs leading to withdrawal from the study vaccine, AEs leading to medically attended visit, AEs leading to death, SAEs, SAEs that are possibly or probably related to vaccine(s), SAEs leading to death, SAEs that are possibly or probably related to vaccine(s)

and leading to death. AEs that were reported as occurring prior to a subject receiving any study vaccine will only be included on the Any AEs listing.

In addition, a summary will be provided of the number and percentage of subjects with each solicited and unsolicited AE and occurrence (number of events) of each solicited and unsolicited AE, classified by system organ class and preferred term within 30 days post-vaccination after any visit, excluding SAEs, for the Overall Safety Set, for each study group.

Missing data will be handled as described in Section 4.3

9.1.3 Adverse Events of Special Interest

Arthritis is the only AESI in this study. Arthritis is defined in section 8.1.6.1 of the protocol. The list of preferred terms corresponding to the diagnosis of arthritis are those included in the MedDRA Standardized MedDRA Queries Narrow "Arthritis". For any new diagnosis of arthritis in a subject, the investigator must complete an ad-hoc eCRF page on arthritis to characterize the AESI.

The number and percentage of subjects identified as having an AESI will be presented by SOC and PT for each study group from date of informed consent through to Day 91. AESI will be presented for the Overall Safety Set.

A listing will be provided for subjects identified as having an AESI.

Missing data will be handled as described in Section 4.3.

9.2 Clinical Laboratory Evaluations

No routine clinical laboratory assessments will be performed per protocol. Only immunogenicity blood samples will be collected in this study (i.e. no routine clinical laboratory assessments will be performed per protocol). Should any local laboratory tests be performed during the study for a subject, abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE (refer to protocol Section 8.1.5) and will be included in AE/SAE summaries.

9.3 Vital Signs

The only vital sign recorded in the eCRF is pre-vaccination body temperature. Body temperature is recorded pre-vaccination at Visit 1 and Visit 3 (the MenACWY group will only have pre-vaccination temperature recorded at Visit 1) and in pDiaries for days 1-7 (excluding the 30 minutes immediately post-vaccination) after each vaccination.

Summary statistics (mean, SD, minimum and maximum) for pre-vaccination body temperature at each visit will be presented by study group for the All Exposed Set. Pre-vaccination body temperature will also be summarized separately for subjects who used analgesic/antipyretic medication within 24 hours before vaccination. Pre-vaccination body temperature will be listed for the All Exposed Set.

9.4 Pregnancy

Female subjects of childbearing potential will have a urine pregnancy test prior to any study vaccine(s) administration.

Pregnancy test results will be displayed in a listing for the All Enrolled Set.

10 References

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Miettinen OS, Nurminen M. Comparative analysis of two rates. *Stat Med*. 1985; 4: 213-226.

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11 Appendices

11.1 Vaccine Administration

Table 9 Vaccine Administration

Type of contact and time point	Study group	Treatment name	Site		
			Location	Directionality[2]	Laterality[3]
Visit 1 (Day 1)	MenABCWY	MenABCWY[4]	Deltoid	Upper or lower	Non-dominant

	rMenBOMV+ACWY_S[5]	rMenB+OMV NZ	Upper Deltoid (approximately 2.5 cm above MenACWY injection)	Upper	Non-dominant
		MenACWY[6]	Lower Deltoid (approximately 2.5 cm below rMenB+OMV NZ injection)	Lower	Non-dominant
	rMenBOMV+ACWY_D[7]	rMenB+OMV NZ	Deltoid	Upper or lower	Non-dominant
		MenACWY[6]	Deltoid	Upper or lower	Dominant
	rMenBOMV	rMenB+OMV NZ	Deltoid	Upper or lower	Non-dominant
	MenACWY	MenACWY[6]	Deltoid	Upper or lower	Non-dominant
Visit 3 (Day 61)	MenABCWY	MenABCWY[4]	Deltoid	Upper or lower	Non-dominant
	rMenBOMV+ACWY_S[5]	rMenB+OMV NZ	Upper Deltoid (approximately 2.5 cm above MenACWY injection)	Upper	Non-dominant
		MenACWY[6]	Lower Deltoid (approximately 2.5 cm below rMenB+OMV NZ injection)	Lower	Non-dominant
	rMenBOMV+ACWY_D[7]	rMenB+OMV NZ	Deltoid	Upper or lower	Non-dominant
		MenACWY[6]	Deltoid	Upper or lower	Dominant
	rMenBOMV	rMenB+OMV NZ	Deltoid	Upper or lower	Non-dominant

[1]Intramuscular (IM)
[2]Directionality is a qualifier for further detailing the location of the vaccine(s) administration (e.g. Upper, Lower)
[3]The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine(s) in the non-dominant arm, an injection in the dominant arm may be performed.
[4]MenABCWY is to be reconstituted as a 0.5 mL solution between MenACWY lyo (lyophilized component) and rMenB+OMV NZ (liquid component) by trained staff.
[5]S refers to administration in the same arm (approximately 2.5 cm apart).
[6]MenACWY is to be reconstituted as a 0.5 mL solution between Men A lyo (lyophilized component) and Men CWY liquid (liquid component) by trained staff.
[7]D refers to administration in 2 different arms.

11.2 Schedule of Study Events

Table 10 List of study procedures

Epoch	*Epoch 001*					
Type of contact	**Visit 1**	**Safety call 1**	**Visit 2**	**Visit 3**	**Safety call 2**	**Visit 4**
Time points	**Day 1**	**Day 15**	**Day 31**	**Day 61**	**Day 75**	**Day 91**
Sampling time points	**Pre-Vacc 1**		**Post-Vacc 1**			**Post-Vacc 2**
Informed consent	●[1]					
Check inclusion/exclusion criteria	●[1]			○		
Collect demographic data	●[1]					
Medical history	●[1]					
History directed physical examination	○					
Physical examination	○			○		
Urine pregnancy test	●[2, 3]			●[2,3]		
Check contraindications and warnings and precautions to vaccination	●			●[4]		
Pre-vaccination body temperature	●			●[4]		
Measure/record height and weight	●[1]					
Study group and treatment number allocation	●					
Recording of administered treatment number	●			●[4]		
Blood sampling (~20 mL)	●[5]		●			●[4]
Vaccine(s) administration	●			●[4]		
Record any concomitant medications/vaccinations	●	●	●	●[4]	●[4]	●[4]
Record any intercurrent medical conditions	●	●	●	●[4]	●[4]	●[4]
Distribution of pDiary	○			○ [4,6]		
Review of pDiary			○	○ [4]		○ [4]
Return of pDiary			○ [6]	○ [4,6]		○ [4,6]
Recording of AEs within 30 minutes post-vaccination	●			●[4]		
Recording of solicited AEs (days 1 to 7 post-vaccination)	●			● [4]		
Recording of unsolicited AEs (days 1 to 30 post-vaccination)	●	●	●	●[4]	●[4]	●[4]
Recording of AEs, SAEs, medically attended AEs, AESI, and AEs leading to withdrawal	●[1]	●	●	●	●	●
Recording of AEs/SAEs related to study participation or to a concurrent GSK medication/vaccine	●[1]	●	●	●	●	●
Recording of SAEs related to study vaccine(s)	●[1]	●	●	●	●	●
Study conclusion						●

[1]Activities that can be performed at a separate visit before Visit 1 (maximum 5 days before the Visit 1). All AEs/SAEs, including those related to study participation or to a concurrent GSK medication/vaccine should be recorded starting from informed consent signature. Inclusion/exclusion criteria should be re-checked prior to vaccination at Visit 1.
[2]For women of childbearing age. The pregnancy test is to be performed locally onsite.
[3]A pregnancy test is mandatory even if performed during a prior separate visit.
[4]This study procedure will not be performed at this time point for the MenACWY group, administered only 1 dose of vaccine at Visit 1 (no Visit 3 performed)
[5]Blood sample collection will be performed before vaccine(s) administration.
6Subjects who receive a single dose of MenACWY only will return their pDiary at Visit 2 (Day 31). All subjects in the other treatment groups will return their first pDiary at Visit 3 (Day 61) and will receive a second pDiary for the remainder of the study. (Amended 15 May 2018)
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
AE = adverse event; AESI = adverse event of special interest; eCRF = electronic case report form; GSK = GlaxoSmithKline; Pre-Vacc: pre-vaccination; Post-Vacc: post-vaccination; SAE = serious adverse event