GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Phase IV, open-label, randomized study to enrol healthy adult volunteers, naïve to any previous meningococcal vaccination or meningococcal disease, aged 18-50 years, to be either vaccinated with GSK MenACWY vaccine (Menveo) or GSK rMenB+OMV NZ vaccine (Bexsero), and serve as donors of human blood for conversion into serum to use in the development, qualification, validation and maintenance of immunological assays and to support preclinical research activities, clinical development and life cycle management of GSK Biologicals vaccines
eTrack study number and Abbreviated Title	207911 (MENB REC 2ND GEN-079 HBS)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Amendment 1 Final: 03 August 2021
Co-ordinating author:	PPD (Biostatistician)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer) PPD (Regulatory Affairs manager) PPD (SERM physician) PPD (Public disclosure representative)
Approved by:	PPD (Lead statistician)

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

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LIST OF ABBREVIATIONS

EoS	End of Study
GSK	GlaxoSmithKline Biologicals SA
hSBA	human Serum Bactericidal Assay
ICF	Informed Consent Form
IM	Intramuscular
SAE	Serious adverse event

1. DOCUMENT HISTORY

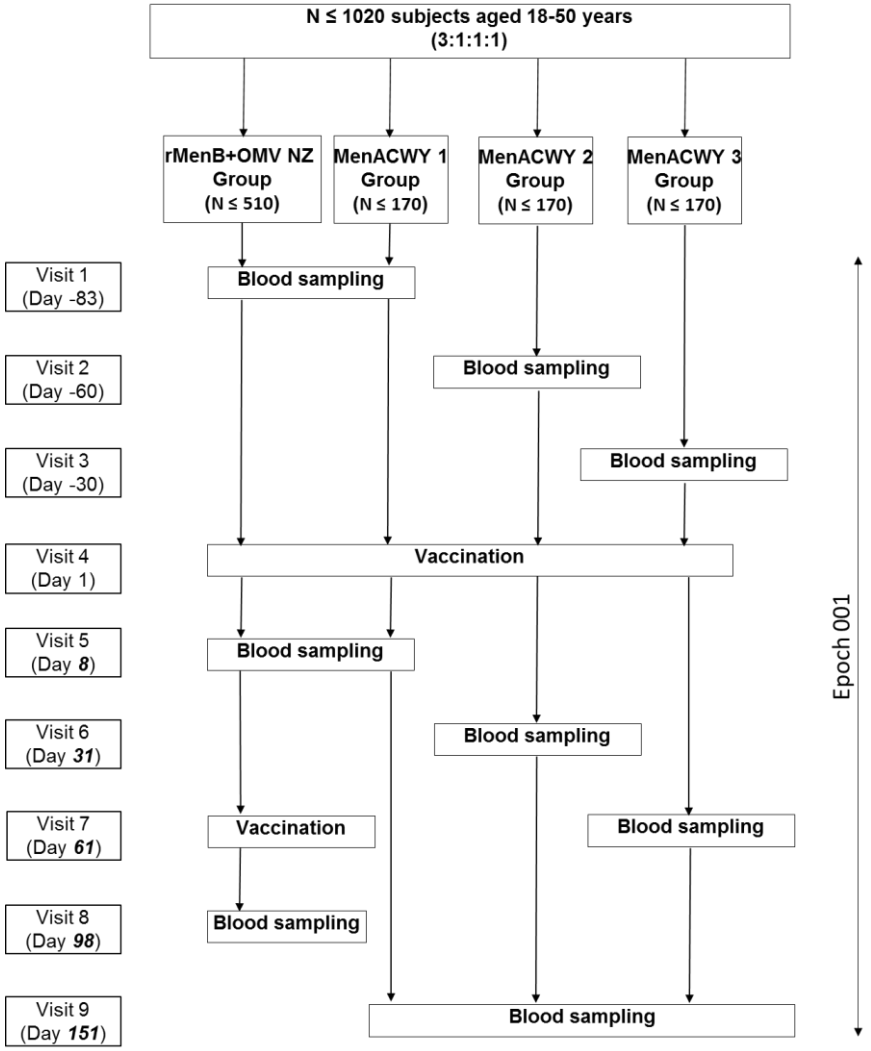
Date	Description	Protocol Version
05-MAR-2021	Amendment 1	Final -19 JAN 2018

This amendment was triggered in order to comply with the National Institute of Health (NIH) requirement for posting clinical results.

2. STUDY DESIGN

The purpose of this study is to source human serum from baseline and post-vaccination blood samples collected from healthy adults exposed to rMenB+OMV NZ or MenACWY vaccine. Figure 1 below shows an overview of the study design

Figure 1 Overview of the study design



rMenB+OMV NZ group: subjects receiving 2 doses of rMenB+OMV NZ vaccine
MenACWY 1, MenACWY 2 and MenACWY 3 groups: subjects receiving 1 dose of MenACWY vaccine

Based on data from completed rMenB+OMV NZ clinical trials, the Day 8 and Day 98 timepoints are sufficient for the rMenB+OMV NZ vaccine arm to provide the target panel of human Serum Bactericidal Assay (hSBA) titres covering the anticipated analytical range. Due to the necessity to have representative hSBA titers that would cover the full targeted analytical range (negative, and positive low, medium and high titers), the MenACWY vaccine arm will be split in 3 groups, with different post-vaccination blood sampling timepoints. To obtain the range of titres for A, C, W and Y hSBA assays, Day 31, Day 61 and Day 151 timepoints are needed based on a previous GlaxoSmithKline Biological SA (GSK) study (Men-ABCWY-Epi-002).

The 3MenACWY groups are also necessary due to large volumes of blood required at each blood draw, because the timing between consecutive blood samplings must comply with the minimum interval, required by local health authorities and guidelines [Australian Red Cross, 2016]. The only way to ensure a blood draw at Day 31, Day 61 and Day 151 timepoints is to have 3 MenACWY groups. The rMenB+OMV NZ vaccine arm will not be split, due to the sufficient interval between the post-vaccinations blood sampling timepoints (Day 8 and Day 98).

Duration of the study is planned over a period of up to 5 years and the enrolment of the subjects is planned as follows:

- Year 1: up to 540 subjects will be enrolled
- Years 2 to 5: up to 120 subjects will be enrolled each study year following year 1

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Protocol Section 5.5), are essential and required for study conduct.

- Experimental design: Phase IV, open-label, randomised, uncontrolled, multi-centric, multi-country study to identify healthy adult volunteers to be vaccinated and serve as donors of human serum. The subjects, 18-50 years of age at the time of informed consent form (ICF) signing, will be randomized in 4 parallel groups, the rMenB+OMV NZ group that will receive rMenB+OMV NZ vaccine administered at a 0,2- month schedule and the MenACWY 1, MenACWY 2 and MenACWY 3 groups, that will receive 1 dose of MenACWY vaccine.
- Duration of the study for individual subjects: For each subject enrolled, there will be a study duration of approximately 6 to 8 months.
  - Epoch 001: Primary starting at Visit 1 (Day -83) and ending at Visit 9 (Day 151)
  - Primary completion Date (PCD): Visit 9 (Day 151) or last visit of Epoch 001 of the last study year

Refer to protocol glossary of terms for the definition of PCD.

- End of Study (EoS): Last subject last visit at Visit 9 (Day 151) of the last study year

Refer to protocol glossary of terms for the definition of EoS.

- Study groups:

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
rMenB+OMV NZ	up to ~510	18 years – 50 years	x
MenACWY 1	up to ~170	18 years – 50 years	x
MenACWY 2	up to ~170	18 years – 50 years	x
MenACWY 3	up to ~170	18 years – 50 years	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups			
		rMenB+OMV NZ	MenACWY 1	MenACWY 2	MenACWY 3
rMenB+OMV NZ (*Bexsero*)	***rMenB+OMV NZ***	x			
MenACWY (*Menveo*)	MenA lyo		x	x	x
	MenCWY liquid				

- Control: uncontrolled
- Vaccination schedule(s):
  - rMenB+OMV NZ group: at Visit 4 and Visit 7, respectively, intramuscular (IM) injection of rMenB+OMV NZ vaccine
  - MenACWY 1, MenACWY 2 and MenACWY 3 groups: at Visit 4, IM injection of MenACWY vaccine
- Treatment allocation:
  - rMenB+OMV NZ group: Up to 270 subjects during the first study year and up to 60 subjects during each of the following study years, 18 through 50 years of age at the time of ICF signing, will receive 2 doses of rMenB+OMV NZ vaccine
  - MenACWY 1, MenACWY 2 and MenACWY 3 groups: Up to 90 subjects, during the first study year and up to 20 subjects during each of the following study years, in each group, 18 through 50 years of age at the time of ICF signing, will receive 1 dose of MenACWY vaccine

  Please refer to Protocol Section 5.2 for a detailed description of the randomisation method.
- Blinding: Open

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule:

Table 4 Sampling schedule

Study groups	Blood donation schedule	Blood sample volume [mL] at each visit
rMenB+OMV NZ	Visit 1; Visit 5 and Visit 8	300
MenACWY 1	Visit 1, Visit 5 and Visit 9	300
MenACWY 2	Visit 2, Visit 6 and Visit 9	300
MenACWY 3	Visit 3, Visit 7 and Visit 9	300

- Type of study: self-contained
- Data collection: Standardised Electronic Case Report Form (eCRF).
- Safety monitoring: serious adverse events (SAEs) will be monitored during the entire study.

3. OBJECTIVES

3.1. Primary objective

- To collect baseline (Visit 1, Visit 2 or Visit 3, depending on the study group) and post vaccination (Visits 5, 8; Visits 5, 9; Visits 6, 9 or Visits 7, 9, depending on the study group) blood sample donations to serve for the development, qualification, validation and maintenance of immunological assays and to support the preclinical research activities, clinical development and life cycle management of GSK Biologicals' vaccines.

Refer to Section 4.1 of this document for the definition of the primary endpoint.

3.2. Secondary objective

- To descriptively assess the safety of each subject given one of the 2 meningococcal vaccines as per the recommended dosage and schedule during their participation in the study.

Refer to Section 4.2 of this document for the definition of the secondary endpoint.

4. ENDPOINTS

4.1. Primary endpoint

- Collection of human blood for conversion into serum to use in the development, qualification, validation and maintenance of immunological assays and to support the preclinical research activities, clinical development and life cycle management of GSK Biologicals' vaccines:
  - at Visit 1, Visit 5 and Visit 8 for the rMenB+OMV NZ group;
  - at Visit 1, Visit 5 and Visit 9; Visit 2, Visit 6 and Visit 9 and Visit 3, Visit 7 and Visit 9 for the MenACWY 1, MenACWY 2 and MenACWY 3 groups, respectively.

4.2. Secondary endpoint

- Assessment of the occurrence of SAEs related to vaccination throughout the study, in all subjects.

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

All subjects in the exposed set who provide safety data

5.2. Criteria for eliminating data from Analysis Sets

5.2.1. Elimination from All 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.

6. STATISTICAL ANALYSES

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 vaccine group.

Frequency distributions of sex and race will be summarized overall and by vaccine group.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccinations will be summarized by vaccine group, vaccination number, and overall. Data will be tabulated for the All Enrolled Set. Additionally, summary statistics of the volume of blood collected per subject will be presented (mean, standard deviation, median, minimum and maximum).

6.3. Analysis of safety

6.3.1. Analysis of safety planned in the protocol

Listings of all SAEs, all related SAEs, and pregnancies will be created. If the number of subjects with at least one SAE is sufficiently large, a Table presenting the number (%) of subjects with at least one SAE may be considered.

6.3.1.1. Clinical Safety Laboratory Investigations

Not applicable.

6.3.1.2. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary. The frequencies and percentages of subjects with concomitant medications that were taken/given prior to the vaccination or blood collection, will be tabulated by vaccine group.

6.4. Analysis of Blood Sample

6.4.1. Analysis of sample tubes planned

The number of subjects with samples and total number of tube samples per visit will be summarized by vaccine group and overall.

7. ANALYSIS INTERPRETATION

All analyses are descriptive.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

All analyses (including interim analysis) will be conducted on clean data.

An interim report will be prepared annually and, at the end of the study, a clinical study report will be prepared, and both will include the following:

- The number of subjects enrolled.
- The number of subjects not meeting inclusion/exclusion criteria.

- The number of subjects that attended each visit.
- The volume of blood collected per subject.
- A listing of all SAEs, all related SAEs, and pregnancies, that occurred during the entire study participation.

An integrated clinical study report containing all data will be written and made available to the investigators.

8.2. Statistical considerations for interim analyses

In order to obtain early data regarding the study objectives and to comply with internal reporting obligations, an interim analysis will be performed yearly on the cumulative data from subjects enrolled up to the respective year. This analysis will present a summary of the number of subjects enrolled, subjects who are compliant with the study visits, the volume of blood collected per subject and also listings of all SAEs with no statistical analysis. Individual listings will also be provided. As the study is not blinded, the interim analysis will be performed by the Sponsor. This analysis will not be used to alter the study conduct nor to conclude on the study objective, there will be no statistical adjustment.

9. CHANGES FROM PLANNED ANALYSES

Not applicable.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

Not applicable.

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

Not applicable, only descriptive statistics will be presented.

11.2. Standard data derivation

Not applicable.

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Phase IV, open-label, randomized study to enrol healthy adult volunteers, naïve to any previous meningococcal vaccination or meningococcal disease, aged 18-50 years, to be either vaccinated with GSK MenACWY vaccine (Menveo) or GSK rMenB+OMV NZ vaccine (Bexsero), and serve as donors of human blood for conversion into serum to use in the development, qualification, validation and maintenance of immunological assays and to support preclinical research activities, clinical development and life cycle management of GSK Biologicals vaccines
eTrack study number and Abbreviated Title	207911 (MENB REC 2ND GEN-079 HBS)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 06-FEB-2018
Co-ordinating author:	PPD (Biostatistician)
Reviewed by:	PPD and PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer) PPD (Regulatory Affairs manager) PPD (SERM physician) PPD (Public disclosure representative)
Approved by:	PPD and PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Scientific writer) PPD (Lead statistical analyst)

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LIST OF ABBREVIATIONS

SAE	Serious adverse event

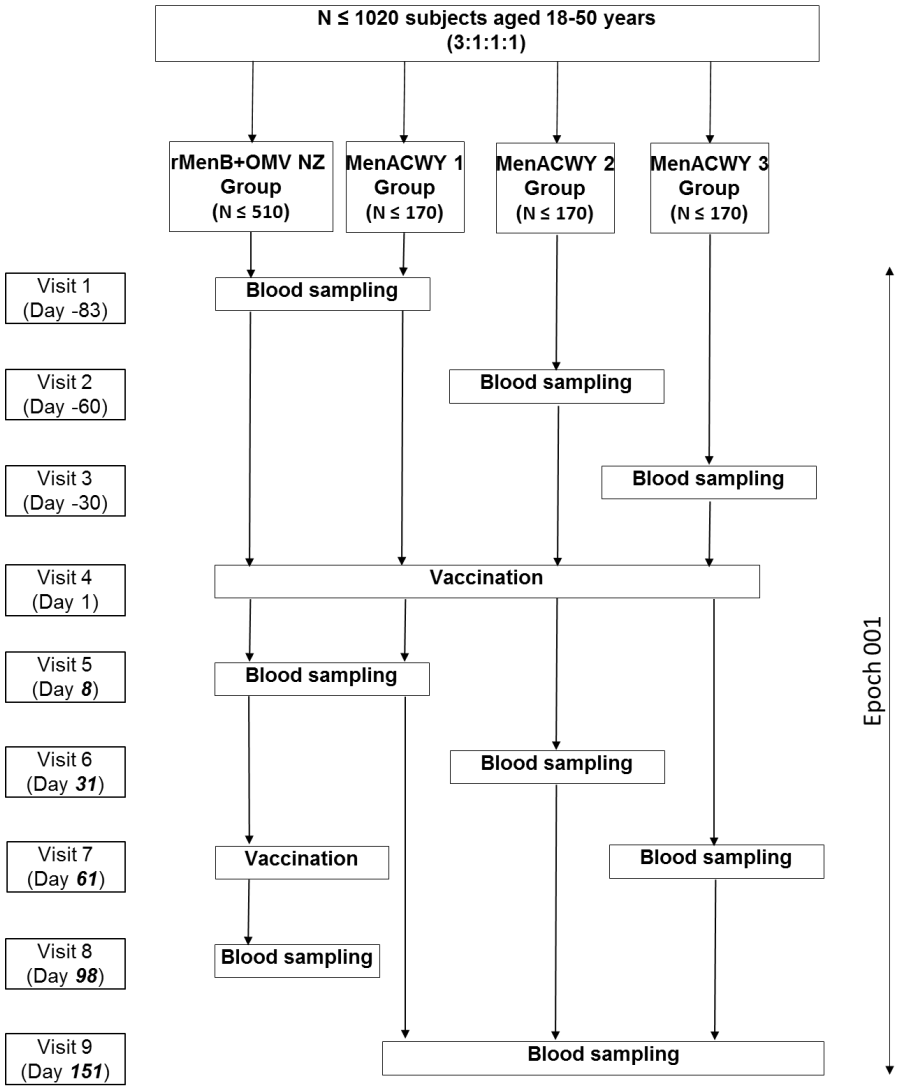
1. DOCUMENT HISTORY

Date	Description	Protocol Version
06-FEB-2018	first version	Final -19 JAN 2018

2. STUDY DESIGN

The purpose of this study is to source human serum from baseline and post-vaccination blood samples collected from healthy adults exposed to rMenB+OMV NZ or MenACWY vaccine. Figure 1 below shows an overview of the study design

Figure 1 Overview of the study design



rMenB+OMV NZ group: subjects receiving 2 doses of rMenB+OMV NZ vaccine
MenACWY 1, MenACWY 2 and MenACWY 3 groups: subjects receiving 1 dose of MenACWY vaccine

Based on data from completed rMenB+OMV NZ clinical trials, the Day 8 and Day 98 timepoints are sufficient for the rMenB+OMV NZ vaccine arm to provide the target panel of hSBA titres covering the anticipated analytical range. Due to the necessity to have representative hSBA titers that would cover the full targeted analytical range (negative, and positive low, medium and high titers), the MenACWY vaccine arm will be split in 3 groups, with different post-vaccination blood sampling timepoints. To obtain the range of titres for A, C, W and W hSBA assays, Day 31, Day 61 and Day 151 timepoints are needed based on a previous GSK study (Men-ABCWY-Epi-002).

The three MenACWY groups are also necessary due to large volumes of blood required at each blood draw, because the timing between consecutive blood samplings must comply with the minimum interval, required by local health authorities and guidelines [Australian Red Cross, 2016]. The only way to ensure a blood draw at Day 31, Day 61 and Day 151 timepoints is to have 3 MenACWY groups. The rMenB+OMV NZ vaccine arm will not be split, due to the sufficient interval between the post-vaccinations blood sampling timepoints (Day 8 and Day 98).

Duration of the study is planned over a period of up to 5 years and the enrolment of the subjects is planned as follows:

- Year 1: up to 540 subjects will be enrolled
- Years 2 to 5: up to 120 subjects will be enrolled each study year following year 1

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Protocol Section 5.5), are essential and required for study conduct.

- Experimental design: Phase IV, open-label, randomised, uncontrolled, multi-centric, multi-country study to identify healthy adult volunteers to be vaccinated and serve as donors of human serum. The subjects, 18-50 years of age (YoA) at the time of ICF signing, will be randomized in four parallel groups, the rMenB+OMV NZ group that will receive rMenB+OMV NZ vaccine administered at a 0,2- month schedule and the MenACWY 1, MenACWY 2 and MenACWY 3 groups, that will receive one dose of MenACWY vaccine.
- Duration of the study for individual subjects: For each subject enrolled, there will be a study duration of approximately 6 to 8 months.
  - Epoch 001: Primary starting at Visit 1 (Day -83) and ending at Visit 9 (Day 151)
  - Primary completion Date (PCD): Visit 9 (Day 151) or last visit of Epoch 001 of the last study year

Refer to protocol glossary of terms for the definition of PCD.

- End of Study (EoS): Last subject last visit at Visit 9 (Day 151) of the last study year

Refer to protocol glossary of terms for the definition of EoS.

- Study groups:

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
rMenB+OMV NZ	up to ~510	18 years – 50 years	x
MenACWY 1	up to ~170	18 years – 50 years	x
MenACWY 2	up to ~170	18 years – 50 years	x
MenACWY 3	up to ~170	18 years – 50 years	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups			
		rMenB+OMV NZ	MenACWY 1	MenACWY 2	MenACWY 3
rMenB+OMV NZ (*Bexsero*)	***rMenB+OMV NZ***	x			
MenACWY (*Menveo*)	MenA lyo		x	x	x
	MenCWY liquid				

- Control: uncontrolled

- Vaccination schedule(s):

  – rMenB+OMV NZ group: at Visit 4 and Visit 7, respectively, intramuscular (IM) injection of rMenB+OMV NZ vaccine

  – MenACWY 1, MenACWY 2 and MenACWY 3 groups: at Visit 4, IM injection of MenACWY vaccine

- Treatment allocation:

  – rMenB+OMV NZ group: Up to 270 subjects during the first study year and up to 60 subjects during each of the following study years, 18 through 50 years of age at the time of ICF signing, will receive 2 doses of rMenB+OMV NZ vaccine

  – MenACWY 1, MenACWY 2 and MenACWY 3 groups: Up to 90 subjects, during the first study year and up to 20 subjects during each of the following study years, in each group, 18 through 50 years of age at the time of ICF signing, will receive 1 dose of MenACWY vaccine

  Please refer to Protocol Section 5.2 for a detailed description of the randomisation method.

- Blinding: Open

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule:

Table 4 Sampling schedule

Study groups	Blood donation schedule	Blood sample volume [mL] at each visit
rMenB+OMV NZ	Visit 1; Visit 5 and Visit 8	300
MenACWY 1	Visit 1, Visit 5 and Visit 9	300
MenACWY 2	Visit 2, Visit 6 and Visit 9	300
MenACWY 3	Visit 3, Visit 7 and Visit 9	300

- Type of study: self-contained
- Data collection: Standardised Electronic Case Report Form (eCRF).
- Safety monitoring: SAEs will be monitored during the entire study

3. OBJECTIVES

3.1. Primary objective

- To collect baseline (Visit 1, Visit 2 or Visit 3, depending on the study group) and post vaccination (Visits 5, 8; Visits 5, 9; Visits 6, 9 or Visits 7, 9, depending on the study group) blood sample donations to serve for the development, qualification, validation and maintenance of immunological assays and to support the preclinical research activities, clinical development and life cycle management of GSK Biologicals' vaccines.

Refer to Section 4.1 of this document for the definition of the primary endpoint.

3.2. Secondary objective

- To descriptively assess the safety of each subject given one of the 2 meningococcal vaccines as per the recommended dosage and schedule during their participation in the study.

Refer to Section 4.2 of this document for the definition of the secondary endpoint.

4. ENDPOINTS

4.1. Primary endpoint

- Collection of human blood for conversion into serum to use in the development, qualification, validation and maintenance of immunological assays and to support the preclinical research activities, clinical development and life cycle management of GSK Biologicals' vaccines:
  - at Visit 1, Visit 5 and Visit 8 for the rMenB+OMV NZ group;
  - at Visit 1, Visit 5 and Visit 9; Visit 2, Visit 6 and Visit 9 and Visit 3, Visit 7 and Visit 9 for the MenACWY 1, MenACWY 2 and MenACWY 3 groups, respectively.

4.2. Secondary endpoint

- Assessment of the occurrence of SAEs related to vaccination throughout the study, in all subjects.

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

All subjects in the exposed set who provide safety data

5.2. Criteria for eliminating data from Analysis Sets

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.

6. STATISTICAL ANALYSES

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 vaccine group.

Frequency distributions of sex and race will be summarized overall and by vaccine group.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccinations will be summarized by vaccine group, vaccination number, and overall. Data will be tabulated for the All Enrolled Set. Additionally, summary statistics of the volume of blood collected per subject will be presented (mean, standard deviation, median, minimum and maximum).

6.3. Analysis of safety

6.3.1. Analysis of safety planned in the protocol

Listings of all SAEs, all related SAEs, and pregnancies will be created. If the number of subjects with at least one SAE is sufficiently large, a Table presenting the number (%) of subjects with at least one SAE may be considered.

6.3.1.1. Clinical Safety Laboratory Investigations

Not applicable.

6.3.1.2. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary. The frequencies and percentages of subjects with concomitant medications that were taken/given prior to the vaccination or blood collection, will be tabulated by vaccine group.

7. ANALYSIS INTERPRETATION

All analyses are descriptive.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

All analyses (including interim analysis) will be conducted on clean data.

An interim report will be prepared annually and, at the end of the study, a clinical study report will be prepared, and both will include the following:

- The number of subjects enrolled.
- The number of subjects not meeting inclusion/exclusion criteria
- The number of subjects that attended each visit.
- The volume of blood collected per subject.
- A listing of all SAEs, all related SAEs, and pregnancies, that occurred during the entire study participation.

An integrated clinical study report containing all data will be written and made available to the investigators.

8.2. Statistical considerations for interim analyses

In order to obtain early data regarding the study objectives and to comply with internal reporting obligations, an interim analysis will be performed yearly on the cumulative data from subjects enrolled up to the respective year. This analysis will present a summary of the number of subjects enrolled, subjects who are compliant with the study visits, the volume of blood collected per subject and also listings of all SAEs with no statistical analysis. Individual listings will also be provided. As the study is not blinded, the interim analysis will be performed by the Sponsor. This analysis will not be used to alter the study conduct nor to conclude on the study objective, there will be no statistical adjustment.

9. CHANGES FROM PLANNED ANALYSES

Not applicable.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

Not applicable.

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

Not applicable, only descriptive statistics will be presented.

11.2. Standard data derivation

Not applicable.