CONFIDENTIAL

207911 (MENB REC 2ND GEN-079 HBS)
Protocol Amendment 4 Final

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'institut 89,
1330 Rixensart, Belgium

Primary Study vaccine(s)/product(s) and number(s)	• GlaxoSmithKline's meningococcal serogroups A, C, W and Y oligosaccharide diphtheria CRM197 conjugate vaccine (*Menveo*) • GlaxoSmithKline's meningococcal group-B vaccine (*Bexsero*)
eTrack study number and Abbreviated Title	207911 (MENB REC 2ND GEN-079 HBS)
EudraCT number	2017-002919-33
Date of protocol	Final Version 1: 07 August 2017
Date of protocol amendment	Amendment 1 Final: 18 September 2017 Amendment 2 Final: 19 January 2018 Amendment 3 Final: 13 September 2019 Amendment 4 Final: 28 April 2020
Title	A sourcing study to collect human biological (serum) samples from healthy adults
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
Co-ordinating author(s) (*Amended, 28 April 2020*)	PPD (*Modis* for GSK Biologicals)
Contributing authors (*Amended, 28 April 2020*)	• PPD (Clinical and Epidemiology Project Lead) • PPD (Clinical Research and Development Lead) • PPD (Study Delivery Lead)

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Contributing authors (*Amended, 28 April 2020*)	• PPD (Clinical Trial Supply Manager, Aixial for GSK Biologicals) • PPD (Project Statistician) • PPD (CLS Read-out Team Leader) • PPD (CLS Study Manager) • PPD (CLS Platform Head) • PPD (CLS Expert Scientist) • PPD (CLS Platform Head) • PPD (Clinical Safety representative) • PPD (Oversight Data Manager) • PPD (Regulatory Affairs ***Specialist***) • PPD (Lead Statistician) • PPD (Local Delivery Leads) • PPD (Study Data Managers) • PPD (Global Patent)

Protocol Amendment 4 Sponsor Signatory Approval

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Sponsor signatory	Michele Pellegrini Clinical and Epidemiology Project Lead, Clinical RDC Italy
Signature	
Date	

Protocol Amendment 4 Rationale

Amendment number:	Amendment 4
Rationale/background for changes:	
This protocol amendment 4 outlines measures that may be applicable during special circumstances (e.g., Coronavirus disease 2019 [COVID-19] pandemic). The purpose of the amendment is to protect participant's welfare, and as far as possible ensure the potential benefit to the participant and promote data integrity.	

Protocol Amendment 4 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' study vaccine(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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Investigator name	_____
Signature	_____
Date	_____
PPD **name, function and title**	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.4.2.

SYNOPSIS

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
Indication	MenACWY (*Menveo*) is indicated in Australia for active immunization of children (from 2 months of age), adolescents and adults to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y. *Menveo* is indicated in Europe for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W and Y, to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations. rMenB+OMV NZ (*Bexsero*) is indicated for active immunization of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B.
Rationale for the study and study design	• Based on an initial assessment of the forthcoming needs of human serum in GlaxoSmithKlines' (GSK) Biologicals' Clinical Laboratory Sciences (CLS) to support *Neisseria meningitidis* human Serum Bactericidal Assays (hSBAs) in the 4- to 5-year horizon, one of the current main gaps identified is related to the validation and maintenance of the hSBAs for each of the serogroups A, C, W, Y and B. These activities require large volumes of matched pairs of pre- and post-vaccination sera from subjects administered GSK meningococcal vaccines. The sera must have hSBA titres to cover the full analytical range of the respective hSBA's, including negative and positive low, medium and high titres, in order to perform all phases of assay development, qualification, validation, and maintenance. The sera collected will also support the biannual conduct of Quality Control, a Health Authority requirement for validated assays. The second main gap to support GSK vaccine development is sufficient supply of sera from vaccinated subjects to be used as samples in preclinical research and clinical development. These gaps

	are only partially covered by any of the existing sourcing activities. Therefore, the purpose of this study is two fold: first, to source human serum from baseline and post-vaccination blood samples collected from healthy adults to be used as control samples in the development, qualification, validation and maintenance of immunological assays supporting the clinical development of GSK Biologicals' vaccines; and second, sera generated in this clinical trial will be used as samples for preclinical research activities, clinical development and life cycle management of other GSK Biologicals' vaccines and to help ensure the quality of the analytical methods for those programs. • Also, it would be preferable to generate large volumes of serum from the same donor, rather than obtaining only different sera with different titres through a large panel of multiple individuals donating small volumes. Current clinical trials will not provide sufficient material to meet such needs, therefore a sourcing study is necessary. • The sera generated with this sourcing study are intended for laboratory and assay use only and are not intended to be used in humans as a product.
Objective(s)	**Primary** • 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. **Secondary** • 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.
Study design	• 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 informed consent form (ICF) signing, will be randomized into one of the 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 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 during each study year following year 1
- 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
- End of Study (EoS): Last subject last visit at Visit 9 (Day 151 of the last study year).
- Study groups:

Synopsis 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

Synopsis 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 MenCWY liquid		x	x	x

- 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
- Blinding: open

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule: Blood samples will be collected from rMenB+OMV NZ group at Visit*s* 1, 5 and 8; from MenACWY 1 group at Visits 1, 5 and 9; from MenACWY 2 group at Visits 2, 6 and 9 and from MenACWY 3 group at Visits 3, 7 and 9
- Type of study: self-contained
- Data collection: Standardised Electronic Case Report Form (eCRF)
- Safety monitoring: SAEs will be monitored during the entire study.

Number of subjects

- Up to 1020 subjects will be enrolled during this study, in the rMenB+OMV NZ, MenACWY 1, MenACWY 2 and MenACWY 3 study groups, in a 3:1:1:1 ratio, respectively.

Endpoint(s)

Primary

- 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; and 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.

Secondary

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

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LIST OF ABBREVIATIONS

ADEM	Acute disseminated encephalomyelitis
AE	Adverse Event
ATEAM	Advanced Temperature Excursion Analysis and Management
BMI	Body Mass Index
°C	Celsius, degrees
CFS	Chronic fatigue syndrome
CLS	Clinical Laboratory Sciences
COVID-19	***Coronavirus Disease 2019***
dL	Deciliters
eCRF	electronic Case Report Form
EoS	End of Study
EoY	End of Study Year
°F	Fahrenheit, degrees
fHbp	Factor H binding protein
g	Grams
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GDS	Global Data Sheet
GSK	GlaxoSmithKline
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug

IRB	Institutional Review Board
ITP	Immune thrombocytopenic purpura
IV	Intravenous
kg	kilogram
LSLV	Last Subject Last Visit
m^2	Square meter
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal serogroups A, C, W and Y
mg	Milligram
Min	Minimum
mL	Milliliters
NadA	Neisserial adhesin Antigen
NHBA	Neisseria Heparin Binding Antigen
NZ PorA	New Zealand serogroup B strain, PorA P1.4
OMV NZ	Outer Membrane Vesicle New Zealand
PCD	Primary Completion Date
PI	Prescribing Information
PO	Per os, i.e., orally
QC	Quality check
rMenB	Meningococcal group B recombinant
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBA	Serum Bactericidal Assay
SBIR	Source Data Base for Internet Randomization

SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SPM	Study Procedures Manual
Vacc	Vaccination
YoA	Years of Age

(Amended, 28 April 2020)

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- Combined oestrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- Contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.
- male condom plus partner use of contraceptive vaginal ring.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

	For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV
Epoch:	An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.

Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Randomisation:	Process of random attribution of treatment/schedule to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.

Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/ product /placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A unique number identifying a treatment to a subject, according to treatment allocation.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GSK group of companies	Generic description
Menveo	Meningococcal (Groups A, C, W and Y) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine
Bexsero	Meningococcal Group B Vaccine

1. INTRODUCTION

1.1. Background

The Serum Bactericidal Assay (SBA) using human serum as the source of complement, is routinely used as immunological assay to measure the induction of functional bactericidal antibodies directed against *Neisseria meningitidis*, as a primary efficacy outcome.

The development and maintenance of human Serum Bactericidal Assays (hSBA) requires the use of high volumes of a large panel of control sera obtained by selecting pre- and post-vaccination serum samples of vaccinated subjects. Control sera are selected as to have a strain-dependent range of titres covering the analytical range of the assays, and preferably no change in controls should take place during a study. A panel of control sera can act as a reference serum panel to test large numbers of strains, in order to further guarantee the maintenance of the quality of the assays in addition to samples required throughout the development and life cycle of the vaccines.

A lack of quality in the assays can lead to improper study conclusions, increased patient risk and protracted regulatory review of potentially lifesaving vaccines.

MenACWY (*Menveo*) is indicated in Australia for active immunization of children (from 2 months of age), adolescents and adults to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y.

Menveo is indicated in Europe for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to Neisseria meningitides groups A, C, W and Y, to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations.

rMenB+OMV NZ (*Bexsero*) is indicated for active immunization of individuals from 2 months of age and older against invasive meningococcal invasive disease caused by *Neisseria meningitidis* serogroup B.

1.2. Rationale for the study and study design

Based on an initial assessment of the forthcoming needs of human serum in GlaxoSmithKlines' (GSK) Biologicals' Clinical Laboratory Sciences (CLS) to support Neisseria meningitidis hSBAs in the 4- to 5-year horizon, one of the current main gaps identified is related to the validation and maintenance of the hSBA for each of the serogroups A, C, W, Y and B. These activities require large volumes of matched pairs of pre- and post-vaccination sera from subjects administered GSK meningococcal vaccines. The sera must have hSBA titres to cover the full analytical range of the respective hSBA's, including negative, and positive low, medium and high titres, in order to perform all phases of assay development, qualification, validation, and maintenance. The sera collected will also support the biannual conduct of Quality Control, a Health Authority requirement for validated assays. The second main gap to support GSK vaccine development is sufficient supply of sera from vaccinated subjects to be used as samples in preclinical research and clinical development. These gaps are only partially covered by any of the existing sourcing activities.

Therefore, the purpose of this study is two-fold: first, to source human serum from baseline and post-vaccination blood samples collected from healthy adults to be used as control samples in the development, qualification, validation and maintenance of immunological assays supporting the clinical development of GSK Biologicals' vaccines; and second, sera generated in this clinical trial will be used as samples for preclinical research activities, clinical development and life cycle management of other GSK Biologicals' vaccines and to help ensure the quality of the analytical methods for those programs.

Also, it would be preferable to generate large volumes of serum from the same donor, rather than obtaining only different sera with different titres through a large panel of multiple individuals donating small volumes. Current clinical trials will not provide sufficient material to meet such needs, therefore a sourcing study is necessary.

The sera generated with this sourcing study are intended for laboratory and assay use only, and will not be used in humans as a product.

1.3. Benefit : Risk Assessment

Please refer to the Prescribing Information (PI) for information regarding the summary potential risks and benefits of *Bexsero* and *Menveo.*

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Bexsero		
Important identified risk: **Fever**	As with other vaccines, fever may occur following vaccination. Fever is listed in the *Bexsero* (see PI).	Acute severe febrile illness constitutes a contraindication (see Section 6.5).
Important potential risk: **Guillain-Barre Syndrome (GBS)**	GBS has been observed with other vaccines. No cases have been reported during the *Bexsero* clinical development program.	The potential risk of events of possible autoimmune aetiology might occur (see Informed Consent Form [ICF]). GBS will be monitored through the SAE collection.
Important potential risk: **Acute disseminated encephalomyelitis (ADEM)**	ADEM has been observed with other vaccines. No cases have been reported during the *Bexsero* clinical development program.	The potential risk of events of possible autoimmune aetiology might occur (see ICF). ADEM will be monitored through the SAE collection.
Important potential risk: **Anaphylaxis and anaphylactic shock**	No cases of anaphylaxis to be related to *Bexsero* have been reported in the *Bexsero* clinical development program. However, one related case of anaphylaxis within 30 minutes was reported in a third party expanded access program (V72_70TP). Allergic reaction (including anaphylactic reaction) is listed (see PI).	Anaphylaxis following the administration of *Bexsero* constitutes a contraindication (see Section 6.5).

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Important potential risk: **Chronic fatigue syndrome (CFS)**	No cases of CFS have been reported from clinical trials nor from post-marketing experience for *Bexsero*. A potential concern was raised with CFS following the vaccination with MenBvac (another Outer Membrane Vesicles [OMV] vaccine) in Norway. The results of a case-control study showed no increased risk [Magnus, 2009].	No specific mitigation: serious adverse event (SAE) collection is part of the study protocol.
Important potential risk: **Decrease of immunogenicity secondary to prophylactic use of paracetamol**	Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either Bexsero or routine vaccines. The effect of antipyretics other than paracetamol on the immune response has not been studied.	No specific risk mitigation in place for this study.
Menveo		
Important potential risk: **Reconstitution errors**	Reports describing medication errors occurred due to administration of the serogroup CWY vaccine component only, without addition of the lyophilized serogroup.	See Section 6.1.
Important potential risk: **Guillain-Barré syndrome**	GBS has been observed with other vaccines. No cases have been reported during the *Menveo* clinical development program.	The potential risk of events of possible autoimmune aetiology might occur (see ICF). GBS will be monitored through the SAE collection.
Important potential risk: **Acute disseminated encephalomyelitis (ADEM)**	ADEM has been observed with other vaccines. Two cases from clinical trials and 5 cases from spontaneous reporting were retrieved from the GSK's global safety database. None has provided sufficient evidence of a causal association between ADEM and *Menveo*.	The potential risk of events of possible autoimmune aetiology might occur (see ICF). ADEM will be monitored through the SAE collection.
Important Potential risk: **Thrombocytopenia**	Immune thrombocytopenic purpura (ITP) has been reported in associations with several licensed vaccines. Two cases related to *Menveo* were reported during the clinical development program, but none has provided a clear association between thrombocytopenia and the vaccine.	ITP will be monitored through the SAE collection.

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Important Potential risk: **Facial Paresis**	Facial paresis was recognised as an important potential risk following the results of a sponsored observational study (V59_34OB) which found an imbalance of cases of facial paresis following vaccination with *Menveo*. No cases of facial paresis were reported from interventional clinical trials.	The potential risk of events of possible autoimmune aetiology that might occur (see ICF). No specific risk mitigation in place in this study.
Important Potential risk: **Vaccination failure (lack of efficacy)**	It is known that a protective immune response may not be generated in every recipient. The number of reports suggestive for vaccination failure reported cumulatively do not suggest a significantly or unexpectedly high rate of vaccine failure.	Proper administration, storage and handling.
Study Procedures		
Risk for large volumes of blood samples	Blood sampling associated risk of discomfort, syncope, dizziness, infection at the site after or during venipuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available (see Section 5.6.9.1). The reasons for deferring the blood draw, including the ones to mitigate potential adverse events linked to the blood draw, are listed in Section 6.7.3.
Risk from lesion sampling.	Needle sampling associated risk of infection, and discomfort related to the procedure.	The potential risk of some temporary discomfort during the sampling procedure and the precautionary use of an anti-bacterial ointment to reduce the risk of infection will be mentioned in the ICF.

1.3.2. Benefit Assessment

Benefits assessments include:

- Potential benefit of receiving the study vaccines, to protect against meningococcal diseases caused by *Neisseria meningitidis* serogroups A, C, W and Y, or serogroup B.
- Contributing to the process of developing new therapies.

1.3.3. Overall Benefit: Risk Conclusion

The potential or identified risks in association with MenACWY and rMenB+OMV NZ vaccines are justified by the potential benefits (prevention) that may be afforded to subject(s) receiving immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis*.

2. OBJECTIVE(S)

2.1. 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 10.1 for the definition of the primary endpoint(s).

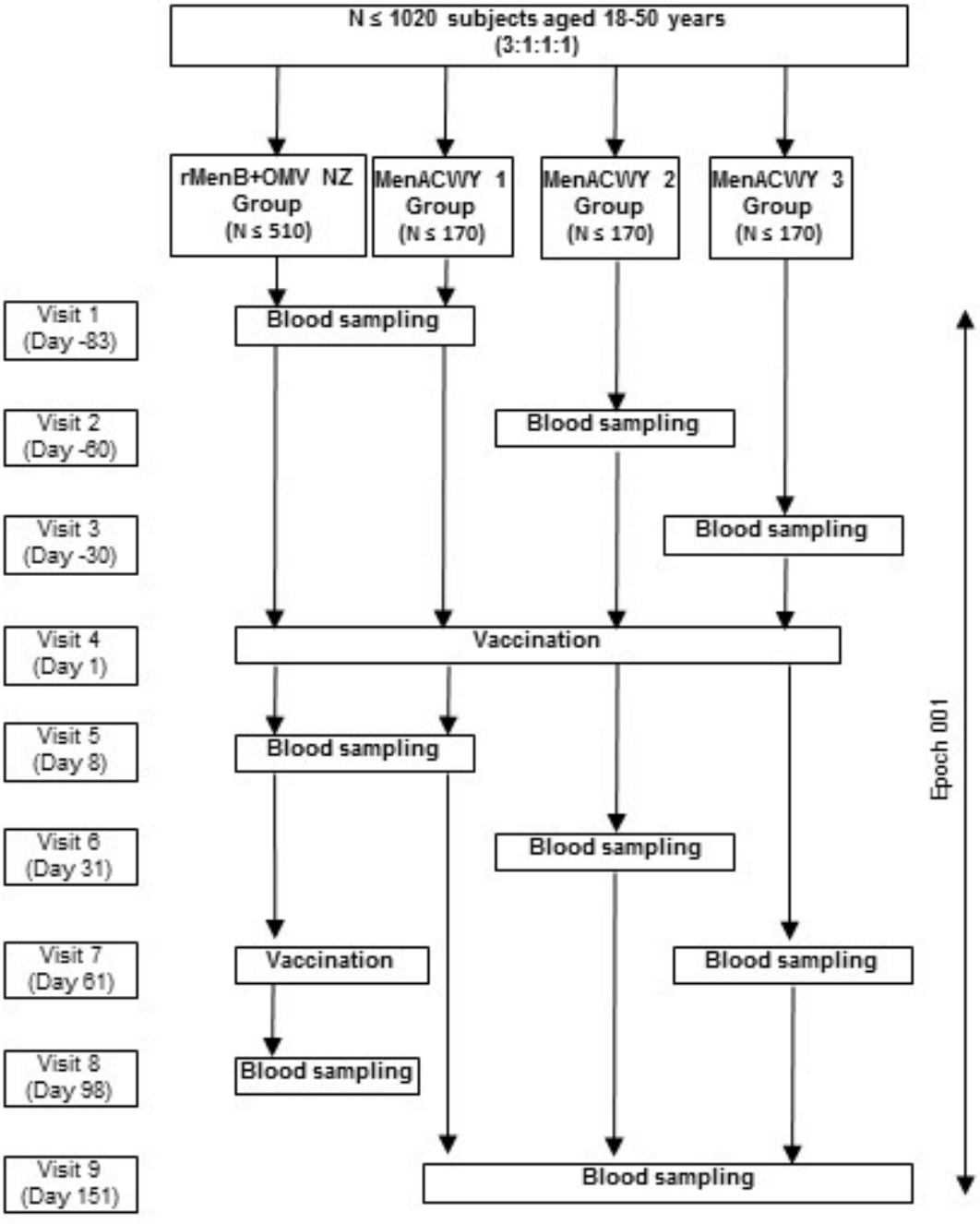
2.2. Secondary objective

- 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 10.2 for the definition of the secondary endpoint(s).

3. STUDY DESIGN OVERVIEW

Figure 1. 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 (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 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 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 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

4. STUDY COHORT

4.1. Number of subjects

During the first study year, the target will be to enrol up to 540 healthy adults, naïve to any previous meningococcal vaccination or meningococcal and gonorrhoea disease**s**, aged 18-50 years at the time of ICF signing, into 4 study groups, in a 3:1:1:1 ratio.

During each of the following four years, the target will be to enrol up to 120 healthy adults, naïve to any previous meningococcal vaccination or meningococcal and gonorrhoea disease**s**, aged 18-50 years at the time of ICF signing, into 4 study groups, in a 3:1:1:1 ratio.

The subjects enrolled during the first study year will be randomized to the rMenB+OMV NZ group (up to 270 subjects) to receive 2 doses of rMenB+OMV NZ vaccine, and the MenACWY groups (MenACWY 1, MenACWY 2 and MenACWY 3; up to 270 subjects in a 1:1:1 ratio), to receive 1 dose of MenACWY vaccine.

The subjects enrolled during each of the following four study years will be randomized to the rMenB+OMV NZ group (up to 60 subjects) to receive 2 doses of rMenB+OMV NZ vaccine, and the MenACWY groups (MenACWY 1, MenACWY 2 and MenACWY 3; up to 60 subjects in a 1:1:1 ratio), to receive 1 dose of MenACWY vaccine.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

1. Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
2. Written informed consent obtained from the subject prior to performing any study specific procedure.
3. A male or female between, and including, 18 and 50 years of age at the time of the first study visit.
4. Healthy subjects as established by medical history and clinical examination before entering into the study.*
5. Subjects must weigh at least 110 pounds (50 kg), but not to present obesity (BMI < 32kg/m^2).

6. Female subjects of non-childbearing potential may be enrolled in the study.
   - Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause.
   - Please refer to the glossary of terms for the definition of menarche and menopause.

7. Female subjects of childbearing potential may be enrolled in the study, if the subject:
   - has practiced adequate contraception for 30 days prior to vaccination, and
   - has a negative pregnancy test on the day of vaccination and
   - has agreed to continue adequate contraception during the entire treatment period and for 1 month, after completion of the vaccination series.

Please refer to the glossary of terms for the definition of adequate contraception.

* Healthy subjects with no medical conditions that, in the opinion of the investigator, prevents the subject from participating in the study.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

Each subject must not have:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
4. Abnormal function of the immune system resulting from:
   - Clinical conditions.
   - Systemic administration of corticosteroids (PO/IV/IM) within 90 days prior to informed consent.
   - Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
5. Received immunoglobulins or any blood products within 180 days prior to informed consent.

6. Received an investigational or non-registered medicinal product within 30 days prior to informed consent.
7. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.
8. Any history of meningococcal vaccination or meningococcal and gonorrhoea diseases.
9. Enrolment in any activity requiring a blood donation greater than 50 mL during the period starting 30 days before the first study visit (Day -83, Day -60 or Day -30) or for the duration of the study period.
10. Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
11. Subjects with blood disorders (e.g., congenital or haemolytic anaemias, haemochromatosis).
12. Subjects with a history of difficulty in providing blood samples (bad veins).
13. Any antibiotic intake 7 days prior to blood collection (please refer to Section 6.7.3: it is possible to delay blood draw 7 days after the last dose of antibiotics).
14. Subjects who donated >450 mL of blood within 60 days prior to any blood collection visits.
15. Subjects who lost >200 mL during a single apheresis or who lost red blood cells on more than one occasion during apheresis within the previous 60 days (please refer to Section 6.7.3).
16. Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
17. Ongoing anaemia as indicated by haemoglobin values below the lower limit of the laboratory-specified reference range (females: haemoglobin < 12.5 g/dl; males: haemoglobin < 13.0 g/dl or as per country specific recommendations/regulations). If the finger prick method demonstrates an anaemia, no further protocol procedures will be performed, and the subject will be referred for appropriate medical management. The subject may participate in this study following therapy and evidence that the anaemia has been resolved.
18. History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
19. Pregnant or lactating female.
20. Female planning to become pregnant or planning to discontinue contraceptive precautions.
21. Any confirmed or suspected immunosuppressive or immunodeficiency condition based on medical history and physical examination (no laboratory testing required).
22. Family history of congenital or hereditary immunodeficiency.
23. Serious chronic illness.
24. History of chronic alcohol consumption and/or drug abuse.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for GCP, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor’s representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.

5.2.2. Randomisation of treatment

An internet randomisation system (Source Data Base for Internet Randomization system, SBIR) will be used for treatment number allocation and for enrolment tracking purposes.

5.2.2.1. Randomisation of supplies

The randomisation of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centres /warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Study group and treatment number allocation

The target will be to enrol up to 1020 eligible subjects who will be randomly assigned to four study groups in a (3: 1: 1: 1) ratio (up to 510: 170: 170: 170 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using the SBIR system. The randomisation algorithm will use a minimisation procedure accounting for centre and study. Minimisation factors will have equal weight in the minimisation algorithm.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding

This is an open-label study with four treatment groups.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5. Outline of study procedures

Table 5 List of study procedures for each study year

Epoch	Epoch 001								
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7*	Visit 8	Visit 9
Timepoint (s)	Day -83	Day -60	Day -30	Day 1	Day 8	Day 31	Day 61	Day 98	Day 151
Sampling timepoint(s)	Pre-Vacc	Pre-Vacc	Pre-Vacc	Vacc I			Vacc II	EoY/EoS	EoY/EoS
Informed consent	●	●	●						
Check inclusion/exclusion criteria	●	●	●						
Collect demographic data	●	●	●						
Medical history	●	●	●						
Physical examination	●	●	●	●	●	●	●	●	●
Urine pregnancy test (locally)	●	●	●	●	●	●	●	●	●
Check contraindications and warnings and precautions to vaccination				O			O		
Measure/ record height	●	●	●						
Measure/ record weight	●	●	●	●	●	●	●	●	●
Check reasons for deferring blood collection	●	●	●		●	●	●	●	●
Study group and treatment number allocation	O	O	O						
Recording of administered treatment number				●			●		
MenACWY vaccine administration				●					
rMenB+OMV NZ vaccines administration				●			●		
Blood sampling for haemoglobin (~ one drop of blood)	●	●	●	●	●	●	●	●	●
Collection of 300 mL blood samples	●	●	●		●	●	●	●	●
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●
Recording of all SAEs and pregnancies	●	●	●	●	●	●	●	●	●
Study Conclusion								●	●

Pre-Vacc: prior to vaccination.
EoY: End of study year.
EoS: end of study.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
Notes: The list of study procedures will be repeated for each study year. Please refer to Section 10.3.
*At Visit 7, the rMenB+OMV NZ group will be scheduled for the second vaccination and should follow the same procedures as those listed at Visit 4, while the MenACWY 3 group will be scheduled for blood sampling and should follow the same procedures as those listed at Visit 6. Please refer to Section 3 for further details on the groups for whom Visits 1, 2, 3 and Visits 5, 6, 7, 8, 9 are applicable.

Whenever possible, the investigator should arrange study visits within the interval described in Table 6, and should keep an interval of at least 90 days between:

- Visit 1 and Visit 5 for group rMenB+OMV NZ and group MenACWY1;
- Visit 2 and Visit 6 for group MenACWY2;
- Visit 3 and Visit 7, and Visit 7 and Visit 9 for group MenACWY3.

Table 6 Intervals between study visits (*Amended, 28 April 2020*)

Groups	Interval	Optimal length of interval
rMenB+OMV NZ	Visit 1 → Visit 4	83 ± 7 days
	Visit 1 → Visit 5	90 + 14 days
	Visit 4 → Visit 5	At least 7 days
	Visit 5 → Visit 7	53 + 14 days
	Visit 7 → Visit 8	37 + 14 days
MenACWY 1	Visit 1 → Visit 4	83 ± 7 days
	Visit 1 → Visit 5	90 + 14 days
	Visit 4 → Visit 5	At least 7 days
	Visit 5 → Visit 9	143 + 14 days
MenACWY 2	Visit 2 → Visit 4	60 ± 3 days
	Visit 2 → Visit 6	90 + 14 days
	Visit 4 → Visit 6	At least 30 days
	Visit 6 → Visit 9	120 + 14 days
MenACWY 3	Visit 3 → Visit 4	30 ± 2 days
	Visit 3 → Visit 7	90 + 14 days
	Visit 4 → Visit 7	At least 60 days
	Visit 7 → Visit 9	90 + 14 days

Note: Under special circumstances, like during COVID-19 pandemic, the length of interval between visits for the collection of biological samples or for the vaccine administration may be extended, please refer to Section 5.6.14

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. Collect demographic data

Record demographic data such as date of birth, sex and race in the subject's eCRF.

5.6.4. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first/the study vaccination in the eCRF.

5.6.5. Physical examination

Perform a physical examination of the subject, including assessment of oral body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest. Weight, height and haemoglobin values will be assessed. Collected information needs to be recorded in the eCRF.

Physical examination will be performed at each study visit.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.6. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test at each study visit. The blood sampling can be collected and the study vaccine(s) may be administered only if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

5.6.7. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.8. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.9. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.9.1. Blood sampling for serum collection

Blood samples will be taken from the rMenB+OMV NZ group at Visit 1, Visit 5 and Visit 8, from the MenACWY 1 group at Visit 1, Visit 5 and Visit 9, from the MenACWY 2 group at Visit 2, Visit 6 and Visit 9, and from the MenACWY 3 group at Visit 3, Visit 7 and Visit 9 (see Section 5.5).

- A volume of 300 mL of whole blood (to provide on average 120 mL of serum) should be drawn from all subjects at each pre-defined timepoint. After processing, serum samples should be kept at preferably -80°C/ –112°F, but –70°C/ –94°F is also acceptable, until shipment. Refer to the SPM for more details on sample storage conditions.
- An overall volume of 900 mL of whole blood will be collected during the entire study period, from each subject.
- The subjects will be observed closely for at least 15 minutes following the blood sampling, with appropriate medical treatment readily available or per local country recommendations and regulations.

5.6.10. Study Vaccine(s) administration

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine(s) will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine(s) administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine(s) administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 6).

The country-specific Prescribing Information for each vaccine will be followed regarding treatment of subjects post vaccination, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.11. Check and record concomitant medication/vaccination

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

5.6.12. Recording of SAEs and pregnancies

- Refer to Section 8.3 for procedures for the investigator to record SAEs and pregnancies. Refer to Section 8.4 for guidelines and how to report SAE and pregnancy to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.

5.6.13. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness
- complete the Study Conclusion screen in the eCRF.

5.6.14. Study procedures during special circumstances (Amended, 28 April 2020)

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (refer to Table 6), then the interval may be extended.***
- ***If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (refer to Table 6), then the interval may be extended.***

5.7. Biological sample handling and analysis

Please refer to the SPM and Central Laboratory Manual for details on Biospecimen Management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with a unique sample identifier, subject and visit numbers.

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 10.4 for the definition of analysis sets to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoint	Study group
Blood donation for hSBA assay development	300	ml	Visit 1, Visit 5 and Visit 8	rMenB+OMV NZ
	300	ml	Visit 1, Visit 5 and Visit 9	MenACWY 1
	300	ml	Visit 2, Visit 6 and Visit 9	MenACWY 2
	300	ml	Visit 3, Visit 7 and Visit 9	MenACWY 3

5.7.3. Laboratory assays

The primary objective of this study is the collection of baseline and post vaccination blood samples from healthy adults to be used 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 for other studies or for development activities. The samples will be measured for concentration of antibodies induced by the administered vaccine, but not as an endpoint.

Further serological tests may be performed to characterise the response to the vaccine, or to support further clinical development and life cycle management of GSK Biologicals vaccines, in case of availability of a sufficient amount of sera.

Additional exploratory testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These assays may not be represented in the objectives/endpoints of the study protocol.

6. STUDY VACCINE(S) AND ADMINISTRATION

6.1. Description of study vaccine(s)

The Quality Control Standards and Requirements for each candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccine(s) are labelled and packed according to applicable regulatory requirements.

Commercial vaccine(s) are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 8 Study vaccine(s)

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
MenACWY	MenA lyo	MenA=10µg CRM197; CRM197=16.7-33.3µg	Lyophilized pellet in a mono dose vial	0.5 ml	1
	MenCWY liquid	MenC=5µg CRM197; MenW=5µg CRM197; MenY=5µg CRM197; CRM197=16-30.8µg	Liquid in a prefilled vial		
rMenB+OMV NZ	rMenB+OMV NZ	rp936-741=50µg; rp287-953=50µg; rp961c=50µg; OMV NZ98/254=25µg; $Al(OH)_3$=1.5mg; Histidine=776µg; NaCl=3.125mg; Sucrose=10mg	Suspension in a glass pre-filled syringe	0.5 ml	2

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

6.2. Storage and handling of study vaccine(s)

The study vaccine(s) must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine(s).

Temperature excursions must be reported in degree Celsius.

Non-IMPs that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor). There is no need for reporting via the Advanced Temperature Excursion Analysis and Management (ATEAM).

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine(s).

6.3. Dosage and administration of study vaccine(s)

Table 9 Dosage and administration

Type of contact and timepoint	Study group	Treatment name	Volume to be administered	Route[1]	Site		
					Location	Directionality[2]	Laterality[3]
Visit 4 (Day 1)	rMenB+OMV NZ	rMenB+OMV NZ	0.5 ml	IM	Deltoid	Upper	Non-dominant
Visit 4 (Day 1)	MenACWY 1	MenACWY	0.5 ml	IM	Deltoid	Upper	Non-dominant
	MenACWY 2						
	MenACWY 3						
Visit 7 (Day 61)	rMenB+OMV NZ	rMenB+OMV NZ	0.5 ml	IM	Deltoid	Upper	Non-dominant

[1]Intramuscular (IM)
[2]Directionality is a qualifier for further detailing the location of the vaccine 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 in the non-dominant arm, an injection in the dominant arm may be performed.

6.4. Replacement of unusable vaccine

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 20% additional vaccine doses will be supplied to replace those that are unusable.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of rMenB+OMV NZ. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.5).

- Anaphylaxis following the administration of vaccine(s).
- Pregnancy (see Section 8.2.1)
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.

The following events constitute contraindications to administration of rMenB+OMV NZ or MenACWY at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C / 99.5°F. The preferred location for digitally measuring temperature in this study will be the oral cavity.*
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.
- * There will be a minimum of 5 consecutive days without fever, before the subject becomes eligible for vaccination.

6.6. Warnings and precautions

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paresthesias and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Syncope (fainting) can occur following, or even before blood sampling, as a psychogenic response to the needle injection. This can be accompanied by bruising and prolonged bleeding. It is important that procedures are in place to avoid injury from faints and that subjects have fluids and some sustenance after the blood draw.

Additional warnings and precautions are listed as exclusion criteria.

Refer to the approved product label/package insert for information on the vaccines in this study.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator or delegate should question the subject about any medications/products taken and vaccinations received by the subject.

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

The investigator will only ask about the concomitant medications/products/vaccines listed below (Section 6.7.2) that were taken/given prior to the vaccination or blood collection visits. For blood products, the investigator should ask if any have been received within 3 months of any vaccination or blood collection and for immunosuppressants or other immune-modifying drugs he/she should ask if any have been received from 6 months prior to vaccination or blood collection. For antibiotics, the investigator should ask if any have been given within 14 days of the vaccination/ blood collection visit and for investigational products, the investigator should ask if any have been received throughout the study.

- Any concomitant vaccination administered in the period starting 14 days before the first dose of study vaccine(s) and ending at the last study visit (Day 98 to Day 151**)**
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol or administered at any time during the study period, for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.

6.7.2. Concomitant medications/products/vaccines that may lead to elimination of the blood sample as a reagent

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may lead to elimination of the blood sample as a reagent.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day (for adult subjects), or equivalent. Inhaled and topical steroids are allowed.
- Any antibiotic intake 7 days prior to blood collection. The subject will have a 7-day delay for blood draw.
- Immunoglobulins and/or any blood products administered within 3 months preceding the dose of study vaccine or blood collection.

6.7.3. Reasons for deferring blood collection

Blood collection will be deferred for the following reasons and will be recorded in the eCRF. After resolution of the condition, or once the protocol-forbidden interval for repeating blood collection is exceeded, the subject may undergo blood collection, as long as it is in within the protocol-specified window.

- Low haemoglobin levels prior to each blood collection. The subjects can donate blood once the levels have returned to normal.
- Current presence of a bleeding disorder.
- Subjects who donated >450 mL of blood within 60 days prior to any blood collection visits.
- Subjects who lost >200 mL during a single apheresis or who lost red blood cells on more than one occasion during apheresis within the previous 60 days.

- Subjects who received any antibiotic within the 7 days before the planned collection of blood. The subjects can donate blood with a 7-days delay after the last dose of antibiotics.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an serious adverse event (SAE) as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Clinical laboratory parameters and other abnormal assessments qualifying as serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. imaging analysis) that are judged by the investigator to be clinically significant will be recorded as SAE if they meet the definition of an SAE (refer to Section 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2. Events or outcomes not qualifying as serious adverse events

8.2.1. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine(s) and may not continue other study procedures.

While pregnancy itself is not considered an SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.4.1 and 8.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine(s) will be reported to GSK Biologicals as described in Section 8.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

8.3. Detecting and recording serious adverse events and pregnancies

8.3.1. Time period for detecting and recording serious adverse events and pregnancies

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine(s) and will continue throughout the study for each subject. See Section 8.4 for instructions on reporting of SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the first study visit and will continue throughout the study for each subject. See section 8.4 for instructions on reporting of pregnancies.

An overview of the protocol-required reporting periods for SAEs and pregnancies is given in Table 10.

Table 10 Reporting periods for collecting safety information

Event	Epoch 001								
	Visit 1 (Day -83)	Visit 2 (Day -60)	Visit 3 (Day -30)	Visit 4 (Day 1)	Visit 5 (Day 8)	Visit 6 (Day 31)	Visit 7 (Day 61)	Visit 8 (Day 98)	Visit 9 (Day 151)
SAEs									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									

8.3.2. Post-Study serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE reporting period defined in Table 10. Investigators are not obligated to actively seek SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study vaccine(s), the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.3. Evaluation of serious adverse events

8.3.3.1. Active questioning to detect serious adverse events

As a consistent method of collecting SAEs, the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous visit?*'

When a SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding a SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms.

8.3.3.2. Assessment of serious adverse events

8.3.3.2.1. Assessment of intensity

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the Adverse Events eCRF will be determined by the investigator as:

Mild:	transient with no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

8.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccine(s) and the occurrence of each SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the SAE could be causally related to a specific vaccine/product administered (i.e investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the SAE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine(s) will be considered and investigated. The investigator will also consult the Prescribing Information for marketed products to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Is there a reasonable possibility that the SAE may have been caused by the study vaccine?

YES	:	There is a reasonable possibility that the study vaccine(s) contributed to the SAE.
NO	:	There is no reasonable possibility that the SAE is causally related to the administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the SAE.

If an event meets the criteria to be determined as ‘serious’ (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine(s), if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.3.2.3. Assessment of outcomes

The investigator will assess the outcome of all SAEs recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.4. Reporting of serious adverse events and pregnancies

8.4.1. Prompt reporting of serious adverse events and pregnancies to GSK Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 11, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 11, once the investigator becomes aware of the pregnancy.

Table 11 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report

*Timeframe allowed after receipt or awareness of the information.
‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.4.2. Contact information for reporting serious adverse events and pregnancies

Study Contact for Reporting SAEs and pregnancies
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs and pregnancies
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.4.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.4.5. Updating of SAE and pregnancy information after removal of write access to the subject's eCRF

When additional SAE and pregnancy information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 11.

8.4.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the study vaccine(s) and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.5. Follow-up of serious adverse events and pregnancies

8.5.1. Follow-up of serious adverse events

8.5.1.1. Follow-up during the study

After the initial SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 11).

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit of the subject.

8.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

8.6. Treatment of serious adverse events

Treatment of any SAE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.7).

8.7. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject. In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times during the study duration.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt (3 telephone calls and a certified letter) to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.

- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she/the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's parent(s)/LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

9.2.2. Subject withdrawal from study vaccine(s)

A 'withdrawal' from the study vaccine(s) refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine(s) may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the study vaccine(s) will be documented on the Vaccine Administration page/screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event.
- Not willing to be vaccinated.
- Other (specify).

10. STATISTICAL METHODS

10.1. 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.

10.2. Secondary endpoint

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

10.3. Determination of sample size

No formal statistical sample size and power calculations will be performed.

The purpose of the study is to support the laboratory with sufficient serum from vaccinated subjects. The two meningococcal vaccines are licensed, and there is no immunogenicity endpoint. Therefore, no formal statistical sample size and power calculations are required to meet the endpoints. The objectives are the collection of serum and descriptive assessment of the safety. Sample size is determined by CLS based on the volumes of sera and the number of individual subjects pre/post vaccination sera that CLS requires (including expected loss due to drop-outs).

Up to 540 subjects, in the first study year, and up to 120 subjects, in each of the following four study years, will be enrolled to identify healthy adult individuals to donate human blood for use in the QC panels for GSK Biologicals' assays.

10.4. Analysis Sets

10.4.1. 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.

10.4.2. All Exposed Set

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

10.5. Conduct of analyses

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

10.5.1. Sequence of analyses

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

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 that attended each visit.
- The volume of blood collected per subject.
- A listing of all 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.

10.5.2. 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.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, public disclosure requirements and publications must be fulfilled.

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with an electronic format in read only mode of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

Interventional studies that do not evaluate vaccines/products are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge or are relevant for patient care, and will be considered for disclosure on the GSK website and in publicly accessible regulatory registry(ies).

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

12. COUNTRY SPECIFIC REQUIREMENTS

All countries will comply with SAE reporting as described in Section 8.4 of the protocol. Additionally, countries and sites will follow all applicable local regulations and guidelines for AE and SAE reporting as required by their respective healthcare authorities and ethics committees.

12.1. Requirements for Germany

EXPLANATORY STATEMENT CONCERNING GENDER DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

For this MENB REC 2ND GEN-079 HBS study, there is no intention to conduct specific analyses investigating the relationship between gender and the safety and efficacy of the *Menveo* and *Bexsero* vaccines. Serum will not be assessed for immunogenicity or efficacy as an endpoint of this trial. Recruitment will include males and females. Females enrolled in this trial will either be of non-childbearing potential, or if they are of childbearing potential, they must practice adequate contraception for 30 days prior to the beginning of the administration of study treatment, have a negative pregnancy test and continue such precautions during the entire study treatment period and for 2 months after completion of the injection series (Refer to the study protocol, Section 4.2 “Inclusion criteria” and Section 4.3 “Exclusion criteria”). The recruitment will be closed to females who are pregnant or lactating. Similarly, patients becoming or deciding to become pregnant during the study must stop the study treatment administrations.

The two vaccines used in this study are licensed and intended for use in both genders, therefore the clinical immunological assays are developed, qualified, validated and maintained using both male and female sera.

13. REFERENCES

Australian Red Cross Blood Service - Eligibility, 2016
http://www.donateblood.com.au/eligibility. Accessed 27 July 2017

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies;
http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005) 'adopted at Community level in May 2006);
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf

Magnus P, Brubakk O, Nyland H, Wold BH, Gjessing HK, Brandt I, Eidem T, Nøkleby H, Stene-Larsen G. Vaccination as teenagers against meningococcal disease and the risk of the chronic fatigue syndrome. *Vaccine*. 2009; 27(1): 23-27.

14. APPENDICES

APPENDIX A CLINICAL LABORATORIES

Table 12 GSK Biologicals' laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart – Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium
GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany	Emil-von-Behring-Str. 76 35041 Marburg Germany

APPENDIX B AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	207911 (MENB REC 2ND GEN-079 HBS)
EudraCT number	2017-002919-33
Amendment number:	Amendment 1
Amendment date:	18 September 2017
Co-ordinating author:	PPD (XPE Pharma & Science for GSK Biologicals)

Rationale/background for changes:

- The detailed title was reworded, to assure consistency with the text of the Protocol, where "rMenB+OMV NZ" is used as vaccine name instead of "Meningococcal B recombinant"
- The name of a contributing author has been updated
- The primary objective was reworded, in order to clarify the timepoints specific for each study group
- The duration of the study for individual subjects has been updated to "approximately 6 to 8 months", as the duration will vary depending on the study group the subject will be assigned to
- In the Synopsis, the sampling schedule was reworded, for clarification purposes
- The List of abbreviations and Glossary of terms were updated
- To avoid misinterpretation, the volume of blood to be collected was changed, from "maximum 300mL" to "300mL"
- The exclusion criteria no. 17 was amended to remove haematocrit values, as haemoglobin values will suffice for detecting anaemia
- The list of study procedures was updated (Table 5), to collect demographic data, have physical examination at each study visit and have different timepoints for recording height and weight of the subjects. As a consequence, Section 5.6. Detailed description of study procedures was updated to reflect the changes in Table 5
- Mandatory wording in Section 5.6.6. Pregnancy test was altered, for consistency with the contraindications for vaccine administration
- The rMenB+OMV NZ vaccine formulation presented in the Vaccine name and Formulation columns in Table 8 was updated, as requested by the German Regulatory team, to ensure consistency with all other Bexsero related documents, clinical and regulatory
- Following comments received from PI, Section 6.6. Warnings and precautions was updated with blood draw warnings and precautions
- Wording containing adverse events (AEs) was deleted, to avoid confusion, as this study will not collect AEs
- Mandatory wording regarding the time period for collecting and recording pregnancies was altered, for consistency with exclusion criteria and study procedures
- Minor edits have been made in alignment with the GSK protocol template.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

COVER PAGE

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 ~~Meningococcal B Recombinant~~ ***rMenB+OMV NZ*** ~~V~~***v***accine (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

Contributing authors

- PPD (Study Delivery Lead***s***)
- PPD (Local Delivery Leads)

SYNOPSIS

Objective(s)

Primary

- To collect baseline (Visit 1, Visit 2 ~~and~~ ***or*** Visit 3, ***depending on the study group***) and post vaccination (~~Visit 5, Visit 6, Visit 7, Visit 8 and Visit 9~~ ***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.

Study design

- Duration of the study for individual subjects: for each subject enrolled, there will be a study duration of approximately ***6 to*** 8 months.

Synopsis 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*)	~~Men B recombinant~~ ***rMenB+OMV NZ***	x			
MenACWY (*Menveo*)	MenA lyo		x	x	x

- Sampling schedule: Blood samples will be collected from ~~all four groups~~ ***rMenB+OMV NZ group*** at Visit***s*** 1, ***5 and 8; from MenACWY 1 group at*** Visit***s 1, 5 and 9; from MenACWY 2 group at*** Visit***s 2, 6 and 9 and from MenACWY 3 group at*** Visit***s 3,*** ~~5, Visit 6, Visit~~7, ~~Visit 8 and Visit~~ and 9.

LIST OF ABBREVIATIONS

~~**pIMD**~~	~~Potential Immune-Mediated Disease~~

GLOSSARY OF TERMS

~~**Potential Immune-Mediated Disease:**~~	~~Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.~~
Protocol amendment:	***The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.***

2.1. Primary objective

To collect baseline (Visit 1, Visit 2 ~~and~~ ***or*** Visit 3, ***depending on the study group***) and post vaccination (~~Visit 5, Visit 6, Visit 7, Visit 8 and Visit 9~~ ***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.

3. STUDY DESIGN OVERVIEW

- Duration of the study for individual subjects: For each subject enrolled, there will be a study duration of approximately ***6 to*** 8 months.
- End of Study (EoS): Last subject last visit at Visit ~~8 or~~ 9 (~~Day 97 or~~ Day 150~~, ending date dependent on the vaccine received by the subject, single dose of MenACWY or 0,2-month schedule of rMenB+OMV NZ~~***)*** of the last study year

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*)	~~Men B recombinant~~ ***rMenB+OMV NZ***	x			
MenACWY (*Menveo*)	MenA lyo		x	x	x
	MenCWY liquid				

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	~~max.~~ 300
MenACWY 1	Visit 1, Visit 5 and Visit 9	~~max.~~ 300
MenACWY 2	Visit 2, Visit 6 and Visit 9	~~max.~~ 300
MenACWY 3	Visit 3, Visit 7 and Visit 9	~~max.~~ 300

~~max., maximum.~~

4.1. Number of subjects

During the first study year, the target will be to enrol up to 540 healthy adults, naïve to any previous meningococcal vaccination or meningococcal ***and gonorrhoea*** disease***s***, aged 18-50 years at the time of ICF signing, into 4 study groups, in a 3:1:1:1 ratio.

During each of the following four years, the target will be to enrol up to 120 healthy adults, naïve to any previous meningococcal vaccination or meningococcal ***and gonorrhoea*** disease***s***, aged 18-50 years at the time of ICF signing, into 4 study groups, in a 3:1:1:1 ratio.

4.3. Exclusion criteria for enrolment

- 17. Ongoing anaemia as indicated by haemoglobin values below the lower limit of the laboratory-specified reference range (females: ~~haematocrit < 38%,~~ haemoglobin < 12.5 g/dl; males: ~~haematocrit < 39%,~~ haemoglobin < 13.0 g/dl or as per country specific recommendations/regulations). If the finger prick method demonstrates an anaemia, no further protocol procedures will be performed, and the subject will be referred for appropriate medical management. The subject may participate in this study following therapy and evidence that the anaemia has been resolved.

5.5. Outline of study procedures

Table 5 List of study procedures for each study year

Epoch	Epoch 001								
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7***	**Visit 8**	**Visit 9**
Timepoint (s)	**Day -83**	**Day -60**	**Day -30**	**Day 1**	**Day 7**	**Day 30**	**Day 60**	**Day 97**	**Day 150**
Sampling timepoint(s)	**Pre-Vacc**	**Pre-Vacc**	**Pre-Vacc**	**Vacc I**			**Vacc II**	**EoY/EoS**	**EoY/EoS**
Informed consent	●	●	●						
Check inclusion/exclusion criteria	●	●	●						
Collect demographic data	●	●	●						
Medical history	●	●	●						
Physical examination	●	●	●	●	●	●	●	●	●
Urine pregnancy test (locally)	●	●	●	●	●	●	●	●	●
Check contraindications and warnings and precautions to vaccination				***O***			***O***		
~~Pre-vaccination body temperature~~				~~●~~			~~●~~		
Measure/record height	●	●	●						
Measure/record ~~height and~~ weight	●	●	●	●	●	●	●	●	●
Check reasons for deferring blood collection	●	●	●		●	●	●	●	●
Study group and treatment number allocation	O	O	O						
Recording of administered treatment number				●			●		
MenACWY vaccine administration				●					
rMenB+OMV NZ vaccines administration				●			●		
Blood sampling for haemoglobin (~ one drop of blood)	●	●	●	●	●	●	●	●	●
Collection of ~~maximum~~ 300 mL blood samples	●	●	●		●	●	●	●	●
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●
Recording of all SAEs and pregnancies	●	●	●	●	●	●	●	●	●
Study Conclusion								●	●

*At Visit 7, the rMenB+OMV NZ group will be scheduled for the second vaccination and should follow the same procedures as those listed at Visit 4, while the MenACWY 3 group will be scheduled for blood sampling and should follow the same procedures as those listed at Visit 6. Please refer to Section 3 for further details on the groups for whom Visits 1, 2, 3 and Visits 5, 6, 7***, 8, 9*** are applicable.

5.6.3. Collect demographic data

Record demographic data such as date of birth, sex and race in the subject's eCRF.

5.6.5. Physical examination

Physical examination ***will be performed*** at each study visit ~~subsequent to the first vaccination visit, will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate~~.

5.6.6. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test ~~prior to any~~ ***at each*** study ~~vaccine administration~~ ***visit***. The ***blood sampling can be collected and the*** study vaccine(s) may ~~only~~ be administered ***only*** if the pregnancy test is negative.

~~**5.6.8. Assess pre-vaccination body temperature**~~

~~The oral body temperature of each subject needs to be measured prior to any study vaccine(s) administration. If the subject has fever [fever is defined as temperature ≥37.5°C/99.5°F regardless the location of measurement]on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 6).~~

5.6.9.1. Blood sampling for serum collection

- A volume of ~~maximum~~ 300 mL of whole blood (to provide on average 120 mL of serum) should be drawn from all subjects at each pre-defined timepoint. After processing, serum samples should be kept at ***preferably -80°C/ –112°F, but*** –70°C/ –94°F ***is also acceptable,*** until shipment. Refer to the SPM for more details on sample storage conditions.
- An overall volume of ~~maximum~~ 900 mL of whole blood will be collected during the entire study period, from each subject.
- The subjects will be observed closely for at least ~~30~~***15*** minutes following the blood sampling, with appropriate medical treatment readily available or per local country recommendations and regulations.

5.7.2. Biological samples

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoint	Study group
Blood donation for hSBA assay development	~~max.~~300	ml	Visit 1, Visit 5 and Visit 8	rMenB+OMV NZ
	~~max.~~300	ml	Visit 1, Visit 5 and Visit 9	MenACWY 1
	~~max.~~300	ml	Visit 2, Visit 6 and Visit 9	MenACWY 2
	~~max.~~300	ml	Visit 3, Visit 7 and Visit 9	MenACWY 3

6.1. Description of study vaccine(s)

Table 8 Study vaccine(s)

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
MenACWY	MenA lyo	MenA=10µg CRM197; CRM197=16.7-33.3µg	Lyophilized pellet in a mono dose vial	0.5ml	1
	MenCWY liquid	MenC=5µg CRM197; MenW=5µg CRM197; MenY=5µg CRM197; CRM197=16-30.8µg	Liquid in a prefilled vial		
rMenB+OMV NZ	~~*Men B Recombinant*~~ ***rMenB+OMV NZ***	~~Men B 961c=50µg; Men B 936-741=50µg; Men B 287-953=50µg; Al(OH)$_3$~~ ***rp936-741=50ug; rp961 c=50ug; OMV NZ98/254=25ug; Al(OH)$_3$=1.5ug; Histidine=776ug; NaCl=3.125mg Sucrose=10mg***	Suspension in a glass pre-filled syringe	0.5ml	2

6.6. Warnings and precautions

Syncope (fainting) can occur following, or even before blood sampling, as a psychogenic response to the needle injection. This can be accompanied by bruising and prolonged bleeding. It is important that procedures are in place to avoid injury from faints and that subjects have fluids and some sustenance after the blood draw.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an ~~adverse event (AE) or~~ serious adverse event (SAE) as provided in this protocol.

8.1.3. Clinical laboratory parameters and other abnormal assessments qualifying as ~~adverse events or~~ serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. imaging analysis) that are judged by the investigator to be clinically significant will be recorded as ~~AE or~~ SAE if they meet the definition of an SAE (refer to Section~~s 8.1.1 and~~ 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as ~~AEs or~~ SAEs.

8.2. Events or outcomes not qualifying as ~~adverse events or~~ serious adverse events

8.2.1. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine(s) ~~but~~ ***and*** may ***not*** continue other study procedures ~~at the discretion of the investigator~~.

While pregnancy itself is not considered an ~~AE or~~ SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an ~~AE or a~~ SAE.

8.3.1. Time period for detecting and recording serious adverse events and pregnancies

The time period for collecting and recording pregnancies will begin at the first ~~receipt of~~ study ~~vaccine(s)~~ ***visit*** and will continue throughout the study for each subject. See section 8.4 for instructions on reporting of pregnancies.

8.3.3.2.3. Assessment of outcomes

The investigator will assess the outcome of all ~~unsolicited AEs (including~~ SAEs~~)~~ recorded during the study as:

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 2**	
eTrack study number and Abbreviated Title	207911 (MENB REC 2ND GEN-079 HBS)
EudraCT number	2017-002919-33
Amendment number:	Amendment 2
Amendment date:	19 January 2018
Co-ordinating author:	PPD (XPE Pharma & Science for GSK Biologicals)
Rationale/background for changes: • Discrepancies have been noted in Study Design Overview and Intervals between study visits Table. Further, day number for Visits 5 to 9 needed to reflect in the following way: Visit 5: Day 8, Visit 6: Day 31, Visit 7: Day 61, Visit 8: 98 and Visit 9: 151.	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

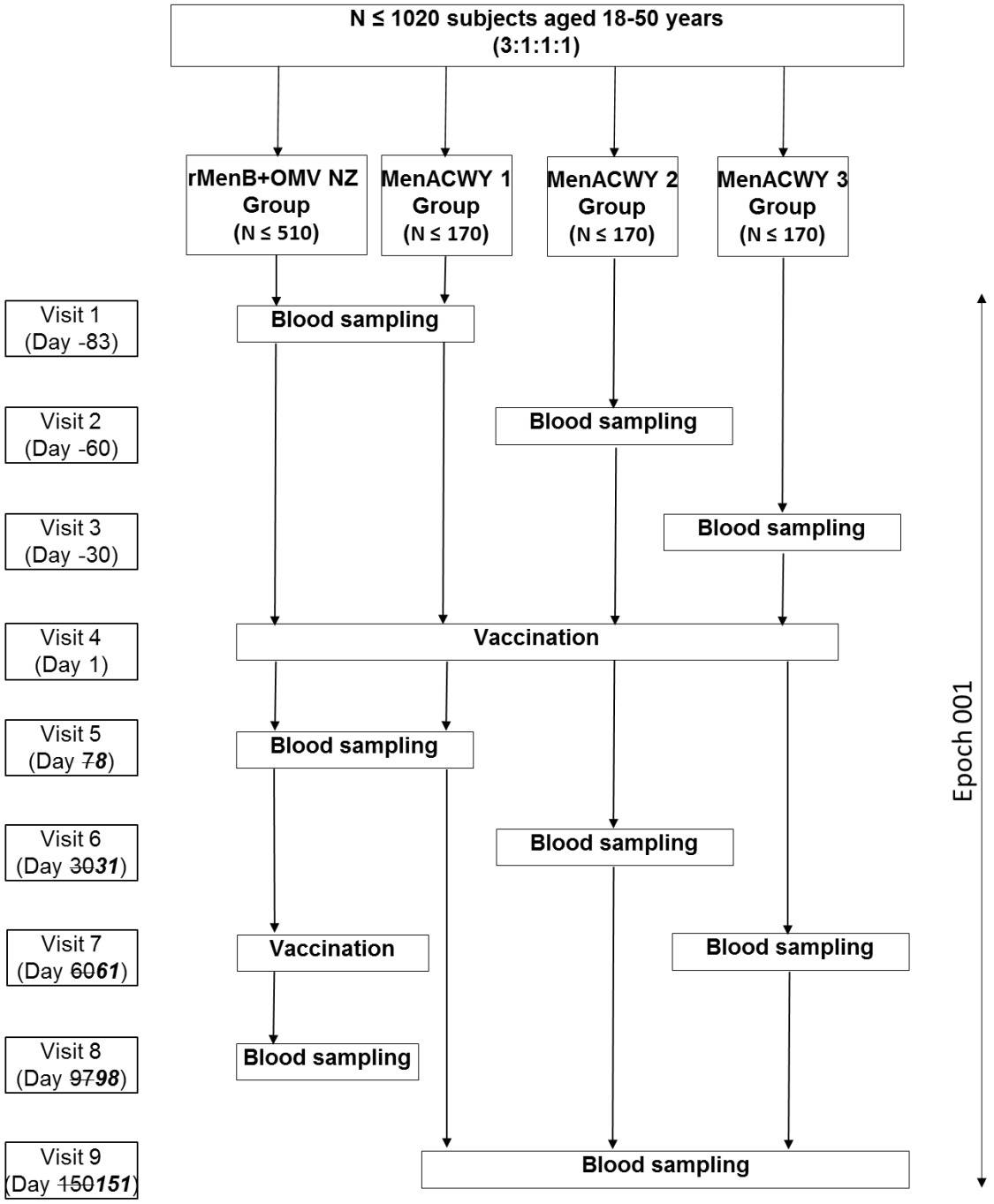
COVER PAGE

Contributing authors	• PPD (Clinical and Epidemiology Project Lead) • PPD (Clinical Research and Development Lead)

SYNOPSIS

Study design	• Epoch 001: Primary starting at Visit 1 (Day -83) and ending at Visit 9 (Day ~~150~~***151***) • Primary completion Date (PCD): Visit 9 (Day ~~150~~***151***) or last visit of Epoch 001 of the last study year • End of Study (EoS): Last subject last visit at Visit 9 (Day ~~150~~ ***151*** of the last study year).

3. STUDY DESIGN OVERVIEW



Based on data from completed rMenB+OMV NZ clinical trials, the Day ~~7~~ ***8*** and Day ~~97~~ ***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 ~~30~~***31***, Day ~~60~~ ***61*** and Day ~~150~~ ***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 ~~30~~***31***, Day ~~60~~***61*** and Day ~~150~~ ***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 ~~7~~ ***8*** and Day ~~97~~***98***).

- 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 ~~150~~***151***)
  - Primary completion Date (PCD): Visit 9 (Day ~~150~~***151***) or last visit of Epoch 001 of the last study year

Refer to glossary of terms for the definition of PCD.

End of Study (EoS): Last subject last visit at Visit 9 (Day ~~150~~***151***) of the last study year

5.5 Outline of study procedures

Table 5 List of study procedures for each study year

Epoch	Epoch 001								
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7*	Visit 8	Visit 9
Timepoint (s)	Day -83	Day -60	Day -30	Day 1	Day ~~7~~*8*	Day ~~30~~*31*	Day ~~60~~*61*	Day ~~97~~*98*	Day ~~150~~*151*
Sampling timepoint(s)	Pre-Vacc	Pre-Vacc	Pre-Vacc	Vacc I			Vacc II	EoY/EoS	EoY/EoS

Table 6 Intervals between study visits

Groups	Interval	Optimal length of interval
rMenB+OMV NZ	Visit 1 → Visit 4	83 ± 7 days
	Visit 1 → Visit 5	90 + 14 days
	Visit 4 → Visit 5	7 + 7 days
	Visit 5 → Visit 7	~~60~~***53*** + 14 days
	Visit 7 → Visit 8	~~30~~***37*** + 14 days
MenACWY 1	Visit 1 → Visit 4	83 ± 7 days
	Visit 1 → Visit 5	90 + 14 days
	Visit 4 → Visit 5	7 + 7 days
	Visit 5 → Visit 9	~~140~~***143*** + 14 days
MenACWY 2	Visit 2 → Visit 4	60 ± 3 days
	Visit 2 → Visit 6	90 + 14 days
	Visit 4 → Visit 6	30 + 14 days
	Visit 6 → Visit 9	120 + 14 days
MenACWY 3	Visit 3 → Visit 4	30 ± 2 days
	Visit 3 → Visit 7	90 + 14 days
	Visit 4 → Visit 7	60 + 14 days
	Visit 7 → Visit 9	90 + 14 days

6.3 Dosage and administration of study vaccine(s)

Table 9 Dosage and administration

Type of contact and timepoint	Study group	Treatment name	Volume to be administered	Route[1]	Site		
					Location	Directionality[2]	Laterality[3]
Visit 4 (Day 1)	rMenB+OMV NZ	rMenB+OMV NZ	0.5 ml	IM	Deltoid	Upper	Non-dominant
Visit 4 (Day 1)	MenACWY 1	MenACWY	0.5 ml	IM	Deltoid	Upper	Non-dominant
	MenACWY 2						
	MenACWY 3						
Visit 7 (Day ~~60~~***61***)	rMenB+OMV NZ	rMenB+OMV NZ	0.5 ml	IM	Deltoid	Upper	Non-dominant

[1]Intramuscular (IM)
[2]Directionality is a qualifier for further detailing the location of the vaccine 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 in the non-dominant arm, an injection in the dominant arm may be performed.

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

- Any concomitant vaccination administered in the period starting 14 days before the first dose of study vaccine(s) and ending at the last study visit (Day ~~97~~***98*** to Day ~~150~~***151***)

8.3.1. Time period for detecting and recording serious adverse events and pregnancies

Table 10 Reporting periods for collecting safety information

Event	Epoch 001								
	Visit 1 (Day -83)	**Visit 2 (Day -60)**	**Visit 3 (Day -30)**	**Visit 4 (Day 1)**	**Visit 5 (Day ~~7~~*8)***	**Visit 6 (Day ~~30~~*31*)**	**Visit 7 (Day ~~60~~*61*)**	**Visit 8 (Day ~~97~~*98*)**	**Visit 9 (Day ~~150~~*151*)**
SAEs									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 3**	
eTrack study number and Abbreviated Title	207911 (MENB REC 2ND GEN-079 HBS)
EudraCT number	2017-002919-33
Amendment number:	Amendment 3
Amendment date:	13 September 2019
Co-ordinating author:	PPD (Modis for GSK Biologicals)
Rationale/background for changes: • To clarify the minimum interval between first (blood draw) study visit and next (vaccination) study visit for all study groups	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

COVER PAGE

Co-ordinating author(s) (Amended 13 September 2019)	• PPD (~~XPE Pharma & Science~~***Modis*** for GSK Biologicals)
Contributing authors (Amended 13 September 2019)	• PPD (Clinical and Epidemiology Project Lead) • PPD (Clinical Research and Development Lead) • PPD PPD (Study Delivery Lead***s***) • PPD (Clinical Trial Supply Manager, Aixial for GSK Biologicals) • PPD (Project Statistician) • PPD (CLS Read-out Team Leader***s***) • PPD (CLS Study Managers) • PPD (Clinical Safety representative) • PPD (Lead Statistician)

- PPD (Local Delivery Leads)
- PPD (Study Data Manager)

5.5 Outline of study procedures

Whenever possible, the investigator should arrange study visits within the interval described in Table 6, ***and should keep an interval of at least 90 days between:***

- ***Visit 1 and Visit 5 for group rMenB+OMV NZ and group MenACWY1;***
- ***Visit 2 and Visit 6 for group MenACWY2;***
- ***Visit 3 and Visit 7, and Visit 7 and Visit 9 for group MenACWY3.*** **(Amended 13 September 2019)**

Table 6 Intervals between study visits (Amended 13 September 2019)

Groups	Interval	Optimal length of interval
rMenB+OMV NZ	Visit 1 → Visit 4	83 ± 7 days
	Visit 1 → Visit 5	90 + 14 days
	Visit 4 → Visit 5	~~7 + 7 days~~ ***At least 7 days***
	Visit 5 → Visit 7	53 + 14 days
	Visit 7 → Visit 8	37 + 14 days
MenACWY 1	Visit 1 → Visit 4	83 ± 7 days
	Visit 1 → Visit 5	90 + 14 days
	Visit 4 → Visit 5	~~7 + 7 days~~ ***At least 7 days***
	Visit 5 → Visit 9	143 + 14 days
MenACWY 2	Visit 2 → Visit 4	60 ± 3 days
	Visit 2 → Visit 6	90 + 14 days
	Visit 4 → Visit 6	~~30 +14 days~~ ***At least 30 days***
	Visit 6 → Visit 9	120 + 14 days
MenACWY 3	Visit 3 → Visit 4	30 ± 2 days
	Visit 3 → Visit 7	90 + 14 days
	Visit 4 → Visit 7	~~60 + 14 days~~ ***At least 60 days***
	Visit 7 → Visit 9	90 + 14 days

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 4**	
eTrack study number and Abbreviated Title	207911 (MENB REC 2ND GEN-079 HBS)
EudraCT number	2017-002919-33
Amendment number:	Amendment 4
Amendment date:	28 April 2020
Co-ordinating author:	PPD (Modis for GSK Biologicals)
Rationale/background for changes: This protocol amendment 4 outlines measures that may be applicable during special circumstances (e.g., COVID-19 pandemic). The purpose of the amendment is to protect participant's welfare, and as far as possible ensure the potential benefit to the participant and promote data integrity.	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

COVER PAGE

Co-ordinating author(s) (*Amended, 28 April 2020*)

- PPD (***Modis*** for GSK Biologicals)

Contributing authors (*Amended, 28 April 2020*)

- PPD (Study Delivery Lead~~s~~)
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- PPD (CLS Read-out Team Leader~~s~~)
- PPD (CLS Study Manager~~s~~)
- PPD (Regulatory Affairs ~~Manager~~***Specialist***)
- PPD PPD (Local Delivery Leads)
- PPD (Study Data Manager***s***)

LIST OF ABBREVIATIONS

COVID-19	*Coronavirus Disease 2019*

5.5 Outline of study procedures

Table 6 Intervals between study visits (*Amended, 28 April 2020*)

Note: Under special circumstances, like during COVID-19 pandemic, the length of interval between visits for the collection of biological samples or for the vaccine administration may be extended, please refer to Section 5.6.14

5.6.14 *Study procedures during special circumstances (Amended, 28 April 2020)*

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (refer to Table 6), then the interval may be extended.***
- ***If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (refer to Table 6), then the interval may be extended.***