Protocol

Study ID: 205416

Official Title of Study: A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.

Date of Document: 12 May 2021

CONFIDENTIAL

205416 [MENB REC 2ND GEN-038 (V72_72)]
Protocol Amendment 4 Final

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

Primary Study vaccine	GlaxoSmithKline Biologicals S.A (GSK)'s Meningococcal Group B Vaccine (*Bexsero* GSK3536829A) GSK's Combined Meningococcal Groups A, B, C, W and Y Vaccine (GSK3536819A)
Other Study vaccine/ product	• GSK's combined Meningococcal Groups A, C, Y and W-135 Conjugate Vaccine (*Menveo,* GSK3536820A) • Placebo
eTrack study number and abbreviated title	205416 [MENB REC 2ND GEN-038 (V72_72)]
Investigational New Drug (IND) numbers	BB-IND-11561 BB-IND-14605
EudraCT number	2019-001666-15
Date of protocol	Final Version 1: 29 January 2015
Date of protocol amendment	Amendment 1 Final: 23 May 2019 Amendment 2 Final: 18 March 2020 Amendment 3 Final: 23 September 2020 Amendment 4 Final: 9 May 2021
Short title	Effectiveness of GlaxoSmithKline Biologicals S.A's Meningococcal Group B and Combined ABCWY Vaccine**s** in Healthy Adolescents and Young Adults.
Title	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
Co-ordinating author **(Amended: 9 May 2021)**	PPD, Scientific Writer
Contributing authors **(Amended: 9 May 2021)**	• PPD, Clinical Research and Development Lead • PPD, Clinical and Epidemiology Project Leader

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Contributing authors (continued) **(Amended: 9 May 2021)**	• PPD and PPD, Study Delivery Leads • PPD, Study Statistician for GSK • PPD, Lead Statistician • PPD - PPD, Oversight Data Manager • PPD, Clinical Trials Supply Manager • PPD, Clinical Laboratory Sciences Read-Out Team Lead • PPD, Clinical Laboratory Sciences Study Manager • PPD, SERM Safety Scientist • PPD, Global Regulatory Affairs • PPD, Across Country Expert, Local Delivery Lead • PPD, US Agent – Global Regulatory Affairs • PPD and PPD, US Medical Affairs Leads • PPD and PPD, Global Patents

GSK Protocol WS v 16.0.1

Protocol Amendment 4 Sponsor Signatory Approval

(Amended 9 May 2021)

eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
IND numbers	BB-IND-11561 BB-IND-14605
EudraCT number	2019-001666-15
Date of protocol amendment	Amendment 4 Final: 9 May 2021
Title	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
Sponsor signatory	Daniela Toneatto, Clinical and Epidemiology Project Lead
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

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 SA.
- 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 study vaccine(s)/product(s) and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- 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 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 in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- 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)/product(s), and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK 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 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	205416 [MENB REC 2ND GEN-038 (V72_72)]
IND numbers	BB-IND-11561 BB-IND-14605
EudraCT number	2019-001666-15
Date of protocol amendment	Amendment 4 Final: 9 May 2021
Title	A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
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 Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.10.3

Study Contact for Reporting SAEs: refer to the local study contact information document.

5. GSK Central Safety Physician On-Call Contact information for Emergency Unblinding

GSK Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.5.6.1.

Refer to the protocol section 7.3.1 for details on emergency unblinding.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Protocol amendment 4	9 May 2021
Protocol Amendment 3	23 September 2020
Protocol Amendment 2	18 March 2020
Protocol Amendment 1	23 May 2019
Protocol Final Version 1	29 January 2015

Amendment 4 [9 May 2021]

Overall Rationale for the Amendment change: The protocol is being amended to document the increase in blood volumes drawn at certain visits (Visit 2 and Visit 6) to improve the serum yield which is critical to evaluate the study endpoints. The allowed windows for study visits during special circumstances have also been widened to maintain subject visit compliance during the COVID-19 pandemic. Additionally, considering that some of the study interventions are combination products constituted of a device and biologic product (pre-filled syringes), the amended protocol provides instructions for collection of safety information related to the use of medical devices. The reporting period for pregnancies has also been updated in line with the current guidelines.

The list of main changes in the protocol with rationale is presented in Table 2 and all changes made to this amendment (including correction of typos) are presented in the amendment history (Refer to Section 12.10.1).

Table 2 List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Synopsis: Overall design Section 5.1: Scientific rationale for study design Section 5.2: Overall design Section 8.4.2.1: Blood sampling for effectiveness and immunogenicity response assessments	The blood volume collected at Visit 2 and Visit 6 has been increased from 25mL to 30 mL.	This change has been made to increase serum yield which is critical to evaluate study endpoints.
Section 8.9: Study procedures during special circumstances	The allowed windows for study visits during special circumstances (Table 17) has been changed from +21 days to +28 days.	To allow for subject visit compliance during the global COVID-19 pandemic.
Section 7.1: Treatments administered Section 8.5.10: Medical device deficiencies Section 12.8: Appendix 8: Definition of medical device AE,	Product category and Type included Implementation of wording on medical device deficiency for combination products for Post Marketing Safety Reporting	In line with the FDA Combination Product Post Marketing Safety Reporting guidance.

Section # and Name	Description of Change	Brief Rationale
adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)		
Synopsis Table 1: Objectives and endpoints Section 4, Table 6: Objectives and endpoints Section 8.4.3: Laboratory assays Section 8.4.4.1: Immunological read-outs Section 10.1: Sample size determination Section 10.1.2.12: Non inferiority of MenABCWY vs rMenB+OMV NZ measured by percentage of subjects with 4-fold rise in hSBA titres against MenB component indicator strains post 2nd dose Section 10.3.4.1: Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ Section 10.3.4.4: Immune response of MenABCWY, rMenB+OMV NZ and MenACWY Section 12.2.2: MenB serum bactericidal assays using exogenous human complement (hSBA) – rMenB + OMV NZ	The NHBA strain has been changed from M07-0241084 to M13520.	The new strain has been approved for use in this study by competent authority.
Section 8.5.6: Reporting of serious adverse events, pregnancies and other events Section 12.5.10.4: Completion and transmission of pregnancy reports to GSK Section 12.6.3: Collection of pregnancy information	The timeframe for submitting pregnancy report to GSK is now 24 hours (changed from 2 weeks)	In line with the pregnancy reporting guidelines
Synopsis: Overall design Section 2: Schedule of activities Section 5.2: Overall design Section 8.10: Decentralised study procedures	Home/ remote visits (subject to allowance by local regulations and quality maintenance of study procedures) can be offered to subjects for the collection of biological samples and/or study intervention administration.	In alignment to the decentralised study procedures.
Section 8.4.3, Laboratory assays (Table 12) Section 12.3 Appendix 3 – Clinical laboratories	The laboratory at Marburg is removed from the list of GSK laboratories.	The laboratory at Marburg has become an external laboratory.

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1. SYNOPSIS

Rationale:

In 2013, the US Food and Drug Administration (FDA) agreed with the Company proposal to evaluate meningococcal B vaccine effectiveness against a large panel of US epidemiologically relevant invasive disease strains of *N. meningitidis* serogroup B in adolescents using serum bactericidal assay*s* with endogenous human complement (enc-hSBA). This panel includes 110 serogroup B strains randomly selected from the original panel of 442 endemic strains identified as appropriately representative of invasive meningococcal serogroup B strains detected in the US by the Centers for Disease Control and Prevention (CDC*)* [Welsch, 2018].

Following licensure of *Bexsero* (rMenB+OMV NZ) in the US in 2015, as required under accelerated approval regulations, GSK was requested to demonstrate effectiveness of *Bexsero* via a post-approval confirmatory trial in US adolescents and adults. To date, there has not been an evaluation completed to assess the vaccine effectiveness of the rMenB+OMV NZ vaccine against the panel (as described above) of the US epidemiologically relevant invasive disease strains of *N. meningitidis* serogroup B.

The investigational MenABCWY combination vaccine is based upon two established GSK vaccines, the quadrivalent meningococcal ACWY conjugate vaccine (*Menveo*) and the multi-component recombinant meningococcal B vaccine (*Bexsero*), for which significant nonclinical and clinical data have been generated and used to support marketing authorisations in US, European Union (EU) and several other countries. The MenABCWY investigational vaccine will be reconstituted from the following two components before administration:

- the MenACWY component lyophilised in vial;
- the MenB liquid component in prefilled syringe.

The MenACWY component contains the same antigens in the same amounts as the commercial *Menveo*, in a lyophilised form. The MenB liquid component is the same formulation as the commercial *Bexsero*.

The primary purpose of this study is hence to demonstrate the vaccine effectiveness using enc-hSBA against a panel of 110 randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains, when administered in a 3-dose (0,2,6-months) or a 2-dose (0,6-months; 0,2-months) schedule as a meningococcal group B vaccine (*Bexsero*) and when administered in a 2-dose (0,6-months) schedule as a combined MenABCWY vaccine.

In addition, the other main objectives of this study are:

- to demonstrate the consistency of immune responses from 3 production lots of the MenACWY component of the MenABCWY vaccine,
- to demonstrate the non-inferiority of a 2-dose series of MenABCWY vaccine versus a single dose of *Menveo* (MenACWY) in terms of immune response to meningococcal serogroups A, C, W and Y,

- to demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine versus *Bexsero* (rMenB+OMV NZ) against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains,
- to assess the safety of all study vaccines administered as per their vaccination schedule to healthy subjects aged 10-25 years.

Objectives and Endpoints:

Synopsis Table 1 Study objectives and endpoints

(Amended: 9 May 2021)

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Section 10.1 for details on continuing the evaluation.	
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)

Objectives	Endpoints
against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots*.	
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine*** To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the **two**-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination. *Criterion:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after:* • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) †

Objectives	Endpoints
vaccination in MenB_0_2_6 group (for 0,2-months schedule	
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month ***12***].
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months)† *Criterion:* *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) † relative to baseline (Day 1, Month 0).
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)

Objectives	Endpoints
months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	• 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: 1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) 2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and

Objectives	Endpoints
	• last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) relative to baseline (Day 1, Month 0). 3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) *4*. hSBA GMRs at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) relative to the baseline (Day 1, Month 0).
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). 2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the: • first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0). 3. hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and

Objectives	Endpoints
	• at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). 4. hSBA GMRs against *N. meningitidis* serogroups A, C, W and Y at: • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and • 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). 5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N. meningitidis serogroup B indicator strains = M14459, 96217, ***M13520*** and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively.

Refer to Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

a post-vaccination hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and

a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

a post-vaccination‡ hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and

a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥ LLOQ

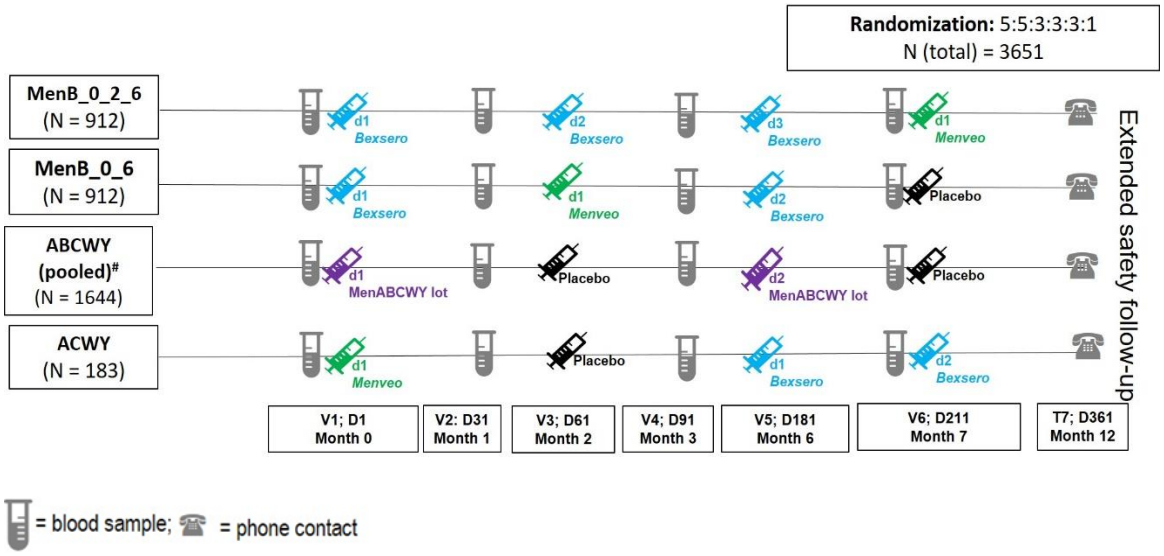
‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

***The primary objective of immunological NI of the MenABCWY vaccine to MenACWY will be evaluated only in subjects without a previous MenACWY vaccination (unprimed). All other primary and secondary objectives will be evaluated in subjects with and without previous MenACWY vaccination (primed/unprimed).

Overall Design:

(Amended: 9 May 2021)

Synopsis Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T = telephone call;
Refer to Table 3 for details on all visits
subjects will receive 2 doses of MenABCWY vaccine with Lot 1 or Lot 2 or Lot 3 of the MenACWY lyophilised vial component of the vaccine. Refer to the study groups description below the figure for details and Figure 1 for the detailed study design overview
Note**s**:
If local regulations allow and if quality of study procedures can be maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Refer to Section 8.10 (decentralised study procedures) for details
Refer to Section 8.9 for information on study procedures during special circumstances

This is a phase III, randomised, controlled, observer-blind, multi-centre study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines.

A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

- **MenB_0_2_6 group:** subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY at Day 211*. Data from this group will be used to assess both the 0,2-months and 0,2,6-months schedules; the 0,2-months schedule will be assessed 1 month after the second rMenB+OMV NZ vaccination administered at Day 61 (Visit 3), and the 0,2,6-months schedule will be assessed 1 month after the third rMenB+OMV NZ vaccination at Day 181 (Visit 5), in the same group.

- **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1and Day 181 and 1 dose of MenACWY vaccine at Day 61 (0,6-months schedule). These subjects will receive 1 dose of the placebo at Day 211*.
- **ABCWY-1****: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*.
- **ABCWY-2**:** subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*.
- **ABCWY-3**:** subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*.
- **ACWY group:** subjects will receive 1 dose of MenACWY at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211*.

  * In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ products administered at Day 211 are not associated with any study objectives/ endpoints (safety assessment conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

  ** (1) A single MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine*;* (2) The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot-to-lot consistency).

  Duration of the study: The study duration is approximately 12 months for each subject.

Synopsis Table 2 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Synopsis Table 3 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	**Visit 2** **Day 31**	**Visit 3** **Day 61**	**Visit 4** **Day 91**	**Visit 5** **Day 181**	**Visit 6** **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; post-vacc = post-vaccination

- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately ***30*** mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination 3 blood sample; approximately ***30*** mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211), prior to the vaccination.

  * Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety follow-up: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 6 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call (Day 361; T7) will also mark the study conclusion. Refer to Table 3 and Section 8.5.3 for details on the safety follow-up.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 3 Schedule of Activities

(Amended 9 May 2021)

Age	*10 through 25 years of age at study start*												
Type of contact	**Visit**	**PC**	***Visit***	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**PC**	**PC**
Visit/Phone call no.	**V1[9]**	**T1**	***V2[9]***	**V3[9]**	**T2**	**V4[9]**	**T3**	**V5[9]**	**T4**	**V6[9]**	**T5**	**T6**	**T7**
Timepoint (s) [refer to Table 4 and Table 5 for visit windows]	**Day 1**	**Day 15**	***Day 31***	**Day 61**	**Day 75**	**Day 91**	**Day 121**	**Day 181**	**Day 195**	**Day 211**	**Day 241**	**Day 301**	**Day 361** ***(ESFU)***
Informed consent[2]	●[1]												
Informed assent, if applicable[2]	○[1]												
Check inclusion/exclusion criteria	●[1]			○[1, 3]				○[1, 3]		○[1, 3]			
Collect demographic data	●[1]												
Study group and treatment number allocation (randomisation)	●[1]												
Medical history	●[1]												
General Physical examination[4]	○[1]												
Symptom-directed physical examination			○	○[1]		○		○[1]		○[1]			
Urine Pregnancy test for females of child-bearing potential	●[1]			●[1]				●[1]		●[1]			
Check contraindications and warnings and precautions to vaccination	○[1]			○[1]				○[1]		○[1]			
Check criteria for temporary delay for enrolment and/ or vaccination and/or blood sampling	○[1]		○	○[1]		○		○[1]		○[1]			
Pre-vaccination body temperature	●[1, 5]			●[1, 5]				●[1, 5]		○[1, 5]			
Blood sampling	●[1]		●			●				●[1]			
Vaccines administration	●			●				●		●[6]			
Recording of administered treatment number	●			●				●		●			

Age	***10 through 25 years of age at study start***												
Type of contact	**Visit**	**PC**	***Visit***	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**PC**	**PC**
Visit/Phone call no.	**V1[9]**	**T1**	***V2[9]***	**V3[9]**	**T2**	**V4[9]**	**T3**	**V5[9]**	**T4**	**V6[9]**	**T5**	**T6**	**T7**
Timepoint (s) [refer to Table 4 and Table 5 for visit windows]	**Day 1**	**Day 15**	***Day 31***	**Day 61**	**Day 75**	**Day 91**	**Day 121**	**Day 181**	**Day 195**	**Day 211**	**Day 241**	**Day 301**	**Day 361** ***(ESFU)***
Post Injection Assessment (30 minutes)	●			●				●		○			
Treatment number allocation for subsequent doses				○				○		○			
Distribution of eDiary	○			○				○					
Review and return of eDiary			●			●				●			
Recording of solicited AEs (Days 1–7 post vaccination) in eDiary	×[5]			×[5]				×[5]					
Recording of unsolicited AEs within 30 days post-vaccination	●	●	●	●	●	●		●	●	●			
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●	●
Recording of any AEs leading to vaccine/study withdrawal, medically attended AEs, SAEs, pregnancies and AESIs[10]	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●[7]	●	●	●	●	●	●	●	●	●	●	●	●
Study Conclusion[8]													●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents.
× is used to indicate a study procedure that will be documented in eDiary.
PC = Phone contact; V = Visit; T=Telephone call; ESFU = Extended safety follow-up; pre-vacc = pre-vaccination; post-vacc = post-vaccination; AE = adverse event; SAE = serious adverse event; AESI = Adverse events of special interest

[1] Procedure to be performed prior to vaccination.

[2] Confirm consent form(s) and informed assent form (if applicable) signed prior to any procedures.

[3] Prior to each vaccination investigator must check eligibility criteria for subsequent vaccination and criteria for vaccination delay as specified in Section 6.3

[4] Physical examination must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log

[5] Fever is defined as body temperature ≥38.0°C (100.4°F). The preferred location for measuring temperature in this study will be the oral route. In case any other route (other than oral) is used for measurement of body temperature/ fever, this also needs to be recorded in the subject's eCRF

[6] Note 3: In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the standard of care (also in line with the ACIP recommendations in the US), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ products administered at Day 211 are not associated with any study objectives/ endpoints (Safety assessment conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

[7] Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a subject/parent(s)/LAR(s) signs the consent form/ assent form (if applicable) to the end of the study

[8] Subjects who terminate the study early are recommended to complete certain study-related procedures (refer to Section 8.8.1)

[9] ***If local regulations allow and if quality of study procedures can be maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Refer to Section 8.10 (decentralised study procedures) for details***

[10] Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 12.5 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 14). In addition, separate COVID-19 specific eCRF form(s) should be completed. ***Refer to Section 8.9 for information related to study procedures during special circumstances***

Whenever possible, the investigator should arrange study visits within the intervals described in Table 4 and Table 5.

Table 4 Intervals between study visits

(Amended: 9 May 2021)

Interval	Length of interval	Allowed interval (Visit window)
Visit 1 → Visit 2	30 days	25 to 44 days after vaccination at V1[1] (from -5 to +14 days)
Visit 1→Visit 3	60 days	55 to 74 days after vaccination at V1[1] (from -5 to +14 days)
Visit 3→Visit 4	30 days	25 to 44 days after vaccination at V3[1] (from -5 to +14 days)
Visit 3→Visit 5	120 days	115 to 134 days after vaccination at V3[1] (from -5 to +14 days)
Visit 5→Visit 6	30 days	25 to 44 days after vaccination at V5[1] (from -5 to +14 days)

[1] Subjects will not be eligible for inclusion in the Per-Protocol Set (PPS) for analysis of immunogenicity if the study visit is performed outside this interval

Refer to Table 17 for intervals between study visits during special circumstances

Table 5 Intervals between study visits and phone calls

Interval	Length of interval	Allowed interval (Visit window)
Visit 1→T1	15 days	12 to 18 days after vaccination at V1 (from -3 to +3 days)
Visit 3→T2	15 days	12 to 18 days after vaccination at V3 (from -3 to +3 days)
Visit 3→T3	60 days	57 to 63 days after vaccination at V3 (from -3 to +3 days)
Visit 5→T4	15 days	12 to 18 days after vaccination at V5 (from -3 to +3 days)
Visit 5→T5	60 days	53 to 74 days after vaccination at V5 (from -7 to +14 days)
Visit 5→T6	120 days	113 to 134 days after vaccination at V5 (from -7 to +14 days)
Visit 5→T7 (ESFU; study end)	180 days	173 to 194 days after vaccination at V5 (from -7 to +14 days)

3. INTRODUCTION

3.1. Study rationale

In 2013, the United States (US) Food and Drug Administration (FDA) agreed with the Company proposal to evaluate meningococcal B vaccine effectiveness against a large panel of the US epidemiologically relevant invasive disease strains of *Neisseria meningitidis* (*N. meningitidis*) serogroup B in adolescents using serum bactericidal assay with endogenous human complement (enc-hSBA). This panel includes 110 serogroup B strains selected from the original panel of 442 endemic strains identified as appropriately representative of invasive meningococcal serogroup B strains detected in the US by the US Centers for Disease Control (CDC) [Welsch, 2018]. Following licensure of *Bexsero* (rMenB+OMV NZ) in the US in 2015, under accelerated approval regulations, GSK was

requested to demonstrate effectiveness of *Bexsero* via a post-approval confirmatory trial in US adolescents and young adults.

The first effectiveness study with GSK's MenB-containing vaccine (investigational MenABCWY vaccine; V102_16) was initiated in 2014 and showed a vaccine effectiveness (test-based) of 67% after 2 doses against the panel of strains described above, as measured by serum bactericidal activity at 1:4 dilution one month post-vaccination [Welsch, 2018]. The V102_16E1 extension study showed a vaccine effectiveness of 71% after 3 doses. To date there has not been an evaluation to assess the vaccine effectiveness of the rMenB+OMV NZ vaccine (*Bexsero*) against this same panel of the US epidemiologically relevant invasive disease strains of *N. meningitidis* serogroup B.

GSK investigational MenABCWY vaccine intended to protect against 5 of the most prevalent serogroups of *N. meningitidis* (A, B, C, W, Y) in humans. This combination vaccine is based upon two established GSK vaccines, the quadrivalent meningococcal ACWY conjugate vaccine (*Menveo*) and the multi-component recombinant meningococcal B vaccine (*Bexsero*), for which significant nonclinical and clinical data have been generated and used to support marketing authorisations in US, European Union (EU) and several other countries. The MenABCWY investigational vaccine will be reconstituted from the following two components before administration:

- the MenACWY component lyophilised in vial;
- the MenB liquid component in prefilled syringe.

The MenACWY component contains the same antigens in the same amounts as the commercial *Menveo*, in a lyophilised form. The MenB liquid component is the same formulation as the commercial *Bexsero*.

The primary purpose of this study is to hence demonstrate the vaccine effectiveness using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains, when administered in a 3-dose (0,2,6-months) or a 2-dose (0,6-months; 0,2-months) schedule as a meningococcal group B vaccine (*Bexsero*) and when administered in a 2-dose (0,6-months) schedule as a combined MenABCWY vaccine.

In addition, the other main objectives of this study are:

- to demonstrate the consistency of immune responses from 3 production lots of the MenACWY component of the MenABCWY vaccine,
- to demonstrate the non-inferiority of a 2-dose series of MenABCWY vaccine versus a single dose of *Menveo* (MenACWY) in terms of immune response to meningococcal serogroups A, C, W and Y,
- to demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine versus *Bexsero* (rMenB+OMV) against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains,
- to assess the safety of all study vaccines administered as per their vaccination schedule to healthy subjects aged 10-25 years.

3.2. Background

(Amended 9 May 2021)

N. meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. *N. meningitidis* infections causing invasive meningococcal disease (IMD) are an important public health concern worldwide due to the substantial morbidity and mortality they cause, as well as the transmissibility of these infections. In healthy individuals, IMD can rapidly progress to serious clinical disease and may be associated with poor outcomes, including fatality in ~10% of cases. While the greatest IMD burden is in infants, there is a second peak of disease in adolescents and young adults.

IMD occurs when the normally asymptomatically carried encapsulated gram-negative bacterium *N. meningitidis* enters the bloodstream, multiplies and causes sepsis. Once the blood-brain barrier is compromised, development of acute bacterial meningitis represents a neurological emergency and necessitates immediate diagnosis and treatment [Heckenberg, 2014]. Although IMD occurs worldwide, incidence varies in different geographic regions, with the highest disease burden observed in low-income countries.

Reliable estimates of the global burden of disease are currently not available, as case definitions differ and surveillance data from many regions are incomplete [Gossger, 2012]. The overall incidence of IMD in European countries ranges from approximately 0.1 to 2.4 cases per 100 000 populations [ECDC, 2016]. In the US, incidence was 0.1 cases per 100 000 population [CDC, 2018].

Ninety percent of meningococcal meningitis and septicaemia are caused by only five *N. meningitidis* serogroups: A, B, C, W and Y. The distribution of serogroups varies geographically and over time. While the disease burden of IMD in higher-income regions, such as Europe and Australia, is largely attributable to serogroup B, in the 'meningitis belt' of sub-Saharan Africa, IMD is predominantly caused by serogroups A and W. In the US, serogroups B, C and Y account for most IMD.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease.

GSK's Meningococcal Groups A, C, Y and W-135 Conjugate Vaccine (*Menveo*) is a meningococcal oligosaccharide conjugate vaccine licensed for active immunisation to prevent IMD caused by *N. meningitidis* serogroups A, C, W-135, and Y. It contains a nontoxic mutant of diphtheria toxin (*Corynebacterium diphtheriae* Cross Reacting Material-197, CRM197) as the carrier protein and has been demonstrated to be highly immunogenic against serogroups ACWY and is well tolerated in all age groups. It has been licensed in more than 60 countries; many of these countries have also approved its use in children. In the EU, the vaccine is indicated for use in individuals 2 years of age and older, and in the US, in individuals 2 months to 55 years of age.

In contrast to the meningococcal serogroups A, C, W and Y, the capsular polysaccharide of serogroup B is poorly immunogenic in humans, possibly due to antigenic similarities in serogroup B carbohydrate moieties to carbohydrates widely expressed on various human cell types. As a result, research has focused on proteins in the outer membrane of meningococci with potential for broad protection against serogroup B as potential antigens for candidate vaccines.

The Meningococcal Group B Vaccine (*Bexsero*, rMenB+OMV NZ) contains three recombinant proteins [factor H binding protein (fHbp), Neisseria adhesin A (NadA), and Neisseria*l* Heparin Binding Antigen (NHBA)], combined with Outer Membrane Vesicles (OMV) components from the New Zealand outbreak strain NZ98/254. rMenB+OMV NZ is immunogenic against the majority of circulating meningococcal serogroup B strains and has acceptable reactogenicity and safety profiles when administered to individuals across age groups.

In January 2013 European marketing authorisation had been granted for *Bexsero* for use in individuals over 2 months of age. In January 2015, based on accelerated approval regulations, FDA licensed *Bexsero* for active immunisation to prevent invasive disease caused by *N. meningitidis* serogroup B in adolescents and young adults 10 through 25 years of age. The vaccine is currently approved in 42 countries worldwide.

Bexsero is indicated for active immunisation against invasive disease caused by *N. meningitidis* serogroup B. Although the meningococcal group B vaccine was developed for individuals aged 2 months and older, the actual age range for which this recommendation extends varies depending on the approval from different health authorities.

With evidence of meningococcal epidemiology changing over time and across geographies [Cohn, 2015; Halperin, 2012; Harrison, 2009], a vaccine with the broadest possible coverage is an important step toward a definitive and global solution for meningococcal disease prevention.

GSK is currently developing a combination vaccine intended to protect against five of the most prevalent serogroups of *N. meningitidis* (A, B, C, W, Y) in humans. The availability of a pentavalent meningococcal vaccine in a single administration would reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide.

Please refer to the current Investigator Brochures for information regarding the pre-clinical and clinical studies of *Bexsero*, *Menveo* and MenABCWY vaccine.

3.3. Benefit/Risk assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of MenABCWY vaccine.

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of *Bexsero* (rMenB+OMV NZ) and *Menveo* (MenACWY).

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

3.3.1. Risk assessment

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational vaccine: rMenB+OMV NZ (*Bexsero*)		
Important potential risk: **Guillain-Barre Syndrome (GBS)**	GBS has been observed with other vaccines. No cases have been identified in the *Bexsero* clinical development program.	The potential risk of events of possible autoimmune aetiology that might occur is mentioned in the Informed Consent Form (ICF). GBS will be monitored through the potential immune-mediated diseases (pIMD) and SAE collection (See Section 12.5.6.2)
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 that can occur is mentioned in the ICF. ADEM will be monitored through the pIMD and SAE collection. (See Section 12.5.6.2)
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 case of anaphylaxis within 30 minutes following vaccination was reported in a third party expanded access program (V72_70TP). Allergic reaction (including anaphylactic reaction) is listed in the *Bexsero* US PI.	Anaphylaxis following the administration of *Bexsero* constitutes a contraindication (see section 7.7). Subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis (see Section **8.2**). Hypersensitivity, including allergy, to any component of vaccines, are exclusion criteria in this study (see Section 6.2).
Important potential risk: **Arthritis**	This potential risk is based on a signal observed for *Bexsero*. Attenuated live virus vaccines (rubella) were reported to be associated with joint-related diseases [Tingle, 1986]. Among inactivated vaccines, different manifestations of arthritis following hepatitis B vaccination (psoriatic arthritis, reactive arthritis, etc.) were described [IOM, 2011]; however no association with meningococcal vaccines has been reported in the literature. One clinical case of juvenile idiopathic arthritis (JIA) possibly related to rMenB+OMV NZ has been observed.	Arthritis will be monitored through the AESI collection (See Section 12.5.6.1).

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational vaccine: MenABCWY		
Important potential risk: **Anaphylaxis, anaphylactic shock**	Anaphylaxis and anaphylactic shock have been observed with other vaccines. No serious cases of anaphylaxis related to MenABCWY have been reported in the MenABCWY clinical development program. Allergic reaction (including anaphylactic reaction) is reported in the MenABCWY IB section “Warning and Precaution".	Anaphylaxis following the administration of MenABCWY constitutes an absolute contraindication to subsequent vaccination (see Section 7.7. The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis. Hypersensitivity, including allergy, to any component of vaccines, are exclusion criteria in this study (see Section 6.2).
MenACWY vaccine (*Menveo*)		
Important Identified risk: **Reconstitution errors**	Cases describing medication errors due to administration of the MenCWY conjugate liquid component only without reconstitution with the MenA conjugate lyophilised component, or due to administration of the MenA conjugate lyophilised component only after reconstitution with a different solvent, have been reported during the MenACWY clinical development program.	In Section 7.1. of the protocol (“Treatment administered”) it is clarified that the 2 vaccine components have to be reconstituted before vaccine injection.
Important potential risk: **GBS**	GBS has been observed with other vaccines. No serious cases have been reported during the MenACWY clinical development program.	The potential risk of events of possible autoimmune aetiology that might occur is mentioned in the ICF. GBS will be monitored through the pIMD and SAE collection (See Section 12.5.6.2)
Important potential risk: **ADEM**	ADEM has been observed with other vaccines. Two serious cases from clinical trials were retrieved from the GSK’s global safety database for MenACWY. None of them has provided sufficient evidence of a causal association between ADEM and MenACWY.	The potential risk of events of possible autoimmune aetiology that can occur is mentioned in the ICF. ADEM will be monitored through the pIMD and SAE collection. (See Section 12.5.6.2)
Important potential risk: **Thrombocytopenia**	Immune thrombocytopenic purpura has been reported in association with several licensed vaccines. One serious case has been reported during the MenACWY clinical development program. This case didn’t provide sufficient evidence of a causal association between thrombocytopenia and MenACWY vaccine.	Immune thrombocytopenic purpura will be monitored through SAE collection (See Section 12.5.6.2).

Important/Potential/Identified/Risk of Clinical Significance	Summary of 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 MenACWY, mainly when administered concomitantly with other vaccines. No cases of facial paresis were reported from interventional clinical trials.	Paralysis of the face is mentioned in the list of side effects in the ICF. Facial paresis will be monitored through SAE collection (See Section 12.5.6.2)
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 of vaccination failure reported cumulatively does not suggest a significantly or unexpectedly high rate of vaccine failure.	No specific risk mitigation in place in this study.
Study Procedures		
Risk of blood sampling	Blood sampling is associated with a risk of syncope, dizziness, local reactions and infection after or during venepuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. Appropriate medical treatment will be readily available.

3.3.2. Benefit assessment

- Receiving GSK's meningococcal vaccines rMenB+OMV NZ, MenABCWY or MenACWY during the study duration may protect against meningococcal IMDs caused by *N. meningitidis* serogroups A, C, W, Y and/or B.
- Medical monitoring and evaluations/assessments associated with this study.
- Contributing to the process of developing new therapies.

3.3.3. Overall Benefit: Risk conclusion

Considering the measures taken to minimise risk to subjects participating in this study, the potential or identified risks in association with rMenB+OMV NZ, MenABCWY and MenACWY are justified by the potential benefits (prevention/treatment) that may be afforded to subject(s) receiving rMenB+OMV NZ and MenACWY or MenABCWY.

4. OBJECTIVE(S) AND ENDPOINT(S)

Table 6 Study objectives and endpoints

(Amended: 9 May 2021)

Objectives	Endpoints
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6-months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)

Objectives	Endpoints
months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	• 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Section 10.1 for details on continuing the evaluation.	
Lot-to-lot consistency: MenABCWY vaccine To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months). *Criterion:* *The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots*.	GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)
Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine*** To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the **two**-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Vaccine effectiveness (Test-based): MenABCWY vaccine To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and • 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Objectives	Endpoints
Criterion: *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	
Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains. *Criterion:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after:* • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • 3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) †
Effectiveness (Responder-based): MenABCWY vaccine To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). *Criterion:* *LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).
Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.

Objectives	Endpoints
	• The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month ***12***].
	Secondary
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months) † <u>Criterion:</u> *Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.*	The percentages of subjects with 4-fold rise** in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the: • last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) † relative to baseline (Day 1, Month 0).
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following:

Objectives	Endpoints
indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) 2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) relative to baseline (Day 1, Month 0). 3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) 4. hSBA GMRs at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) relative to the baseline (Day 1, Month 0).
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). 2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:

Objectives	Endpoints
	• first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0). 3. hSBA GMTs against *N. meningitidis serogroups* A, C, W and Y at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1). 4. hSBA GMRs against *N. meningitidis serogroups* A, C, W and Y at: • 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and • 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0). 5. The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at baseline (Day 1, Month 0) and: • at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and • at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest.

N. meningitidis serogroup B indicator strains = M14459, 96217, ***M13520*** and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively.

Refer to Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

a post-vaccination hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and

a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

a post-vaccination‡ hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and

a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥ LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

***The primary objective of immunological NI of the MenABCWY vaccine to MenACWY will be evaluated only in subjects without a previous MenACWY vaccination (unprimed). All other primary and secondary objectives will be evaluated in subjects with and without previous MenACWY vaccination (primed/unprimed).

5. STUDY DESIGN

5.1. Scientific rationale for study design

(Amended 9 May 2021)

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the US.

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of ***N.*** *meningitidis* (A, B, C, W, Y) in humans.

Hence, along with the licensed MenB vaccine (*Bexsero*), this Phase III study will also assess the safety, effectiveness, and immunogenicity of the investigational MenABCWY vaccine.

Rationale for effectiveness assessment

As mentioned above, one of the primary purposes of this study is to evaluate the effectiveness of 2 or 3 doses of rMenB+OMV NZ and of 2 doses of the MenABCWY vaccines in healthy adolescents and young adults by measuring the bactericidal activity against 110 endemic US *N. meningitidis* serogroup B strains using an endogenous complement human Serum Bactericidal Assay (enc-hSBA), when compared to a control. Sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA as a control for test-based effectiveness assessment. The overall vaccine effectiveness (VE) against all 110 strains combined will be computed by means of a generalised linear model. For additional details see statistical analysis section (Section 10).

Rationale for lot-to-lot consistency assessment

MenABCWY is a reconstituted vaccine with the lyophilised 'ACWY component' and liquid rMenB+OMV NZ. The MenB component has the same formulation as the commercial *Bexsero*. To demonstrate that the lots of the investigational MenABCWY vaccine are adequately representative of the formulation intended for marketing, equivalence will be assessed for 3 different lots of the ACWY component of the ABCWY vaccine.

Rationale for non-inferiority assessment of MenABCWY vs MenACWY and rMenB+OMV NZ

The study aims to also demonstrate that the investigational combination MenABCWY vaccine is not inferior to a licensed MenACWY vaccine (*Menveo*) and a licensed MenB vaccine (*Bexsero*) which are part of the current standards of care in the US for prevention of invasive disease caused by *N. meningitidis* serogroups A, C, W, Y and by *N. meningitidis* serogroup B, respectively.

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)) ***and ELISA (or equivalent), approximately 30 mL whole blood will be collected at Visit 2 and Visit 6 and approximately*** 25 mL whole blood will be collected at Visit 4. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA, ***and ELISA (or equivalent)***.

Blood samples are taken from all subjects irrespective of the testing status in order to maintain the study blind. Refer to Section 8.4.2.1 for further details.

Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims to demonstrate the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has also been added to better characterize the VE with an alternative dose regimen as a post approval requirement from the US FDA.

Note: The rMenB+OMV NZ in the ACWY group is administered in a 0,1-months schedule. This interval is within the recommendations in the summary of product characteristics of *Bexsero* and helps in maintaining the blind. No objectives are associated with this schedule of rMenB+OMV NZ.

MenABCWY: A number of different vaccine formulations were evaluated in MenABCWY Phase I and II clinical studies. The formulation with the same active ingredient composition as the rMenB+OMV NZ (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the investigational MenABCWY vaccine. Two doses administered 6 months apart (0,6-months) is considered the optimal dosing schedule, based on serogroup B immunogenicity results from MenABCWY Phase II clinical studies.

MenACWY: As a comparator for serogroup A, C, W, and Y vaccine effectiveness and immune responses, a single dose of MenACWY vaccine is administered to subjects in the ACWY group. To conform with the standard of care (also in alignment with current ACIP routine immunisation recommendations in US), subjects in the MenB_0_2_6 and MenB_0_6 groups will also receive a dose of MenACWY at Day 211 and Day 61, respectively.

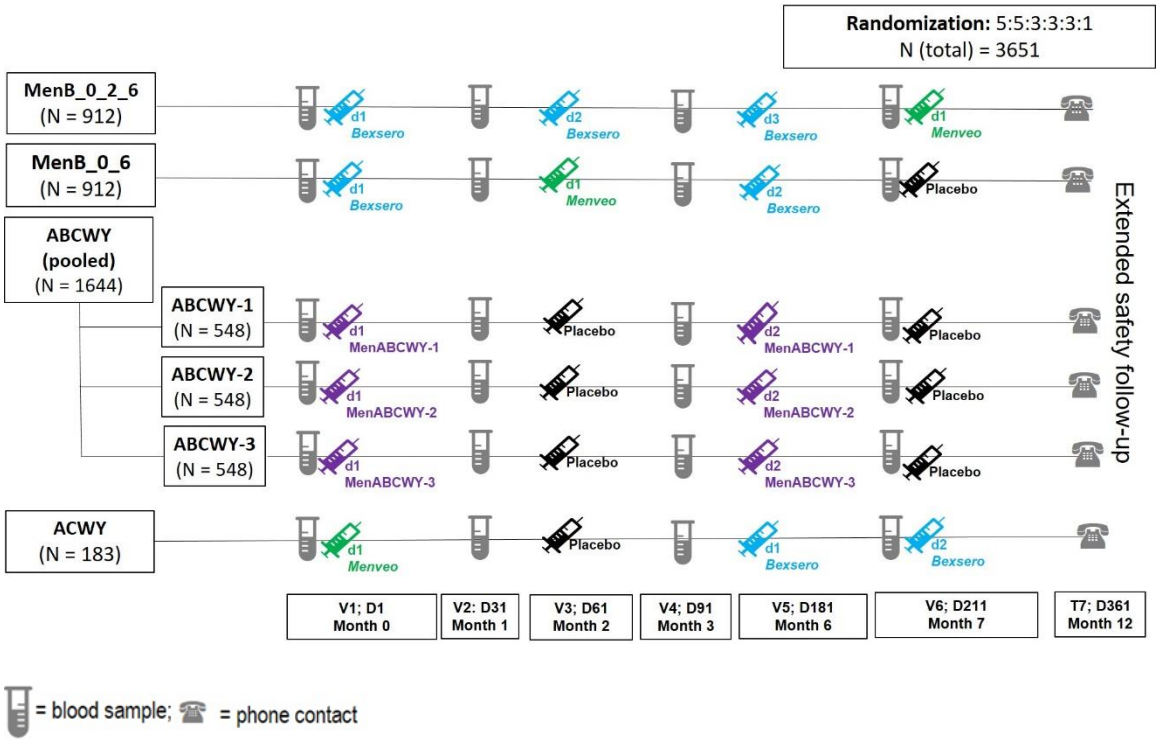
5.1.1. Rationale for the use of placebo

For this study, a placebo (saline solution) will be administered as presented in Figure 1. A placebo is the only available option to minimize possible introduction of reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to subjects assigned to either of the ***six*** study groups.

5.2. Overall design

(Amended 9 May 2021)

Figure 1 Study design overview



N = number of subjects***;*** d = dose; V = visit; D = day***;*** T=Telephone call
Refer to Table 3 for details on all visits
Note***s***:
If local regulations allow and if quality of study procedures can be maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Refer to Section 8.10 (decentralised study procedures) for details
Refer to Section 8.9 for information on study procedures during special circumstances

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 schedule of activities (Section 2), are essential and required for study conduct.

- Type of study: self-contained
- Experimental design: This is a phase III, randomised, controlled, observer-blind, multi-centre study to evaluate effectiveness, immunogenicity and safety of rMenB+OMV NZ and MenABCWY vaccines. A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:
  - **MenB_0_2_6 group**: subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY vaccine at Day 211*****. Data from this group will be used to assess both the 0,2-months and 0,2,6-months schedules; the 0,2-months schedule will be assessed 1 month after the second rMenB+OMV NZ vaccination administered at Day 61 (Visit 3), and the 0,2,6-months schedule will be assessed 1 month after the third rMenB+OMV NZ vaccination at Day 181 (Visit 5), in the same group.
  - **MenB_0_6 group**: subjects will receive 2 doses of rMenB+OMV NZ at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZ, 0,6-months schedule). These subjects will receive 1 dose of placebo at Day 211*.
  - **ABCWY-1**:** subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*.
  - **ABCWY-2**:** subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*.
  - **ABCWY-3**:** subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*.
  - **ACWY group**: subjects will receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211*.

  ***** In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ products administered at Day 211 are not associated with any study objectives/ endpoints (*s*afety assessment conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

** (1) A MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine; (2) The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot-to-lot consistency).

- Duration of the study: The study duration is approximately 12 months for each subject.
- Primary completion Date (PCD): Day 361; T7.

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = T7). If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to glossary of terms for the definition of EoS.

- Study groups:

Table 7 Study groups and treatment foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name
MenB_0_2_6	912	10 – 25 y	*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
MenB_0_6	912		*Bexsero* (Injection)	rMenB+OMV NZ
			Menveo (Injection)	MenACWY
			Placebo (Injection)	NaCl
ABCWY-1	548		MenABCWY (with Lot 1 of ACWY) (Injection)	MenABCWY-1
			Placebo (Injection)	NaCl
ABCWY-2	548		MenABCWY (with Lot 2 of ACWY) (Injection)	MenABCWY-2
			Placebo (Injection)	NaCl
ABCWY-3	548		MenABCWY (with Lot 3 of ACWY) (Injection)	MenABCWY-3
			Placebo (Injection)	NaCl
ACWY	183		*Menveo* (Injection)	MenACWY
			Placebo (Injection)	NaCl
			Bexsero (Injection)	rMenB+OMV NZ

Table 8 Overview of study design: Vaccination and Blood Draw Schedule

Visits **Study Day**	**Visit 1** **Day 1**	**Visit 2** **Day 31**	**Visit *3*** **Day 61**	**Visit *4*** **Day 91**	**Visit *5*** **Day 181**	**Visit *6*** **Day 211**
Group **MenB_0_2_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	rMenB+OMV NZ	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample MenACWY
Group **MenB_0_6** **N=912**	Pre-vacc Blood sample rMenB+OMV NZ	Post-vacc 1 Blood sample	MenACWY	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample Placebo
Group **ABCWY-1** **N=548**	Pre-vacc Blood sample MenABCWY-1	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-1	Post-vacc 3 Blood sample Placebo
Group **ABCWY-2** **N=548**	Pre-vacc Blood sample MenABCWY-2	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-2	Post-vacc 3 Blood sample Placebo
Group **ABCWY-3** **N=548**	Pre-vacc Blood sample MenABCWY-3	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	MenABCWY-3	Post-vacc 3 Blood sample Placebo
Group **ACWY** **N=150**	Pre-vacc Blood sample MenACWY	Post-vacc 1 Blood sample	Placebo	Post-vacc 2 Blood sample	rMenB+OMV NZ	Post-vacc 3 Blood sample rMenB+OMV NZ

N = number of subjects; Pre-vacc = pre-vaccination; Post-vacc = post-vaccination

- Treatment allocation: At Day 1, prior to the study vaccination, subjects will be randomised to 1 of the 6 study groups according to a 5:5:3:3:3:1 ratio.
- Blinding: Observer-blind. Kindly refer to Section 7.3 for details on blinding and unblinding procedures.
- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately ***30*** mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination-3 blood sample; approximately ***30*** mL).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects of child-bearing potential at Visit 1 (Day 1), Visit 3 (Day 61), Visit 5 (Day 181) and Visit 6 (Day 211) prior to the vaccination.

  *Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
- Data collection: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).
- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call 6 months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call (Day 361; T7) will also mark the study conclusion. Refer to Table 3 and Section 8.5.3 for details on the safety follow-up.

5.3. Number of subjects

A total of 3651 subjects will be randomised in a ratio of 5:5:3:3:3:1; 912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY groups and 183 in ACWY group. Assuming a 25% drop-out rate, this should provide approximately 684 evaluable subjects in the MenB groups, 411 evaluable subjects in the ABCWY groups and 137 evaluable subjects in the ACWY group.

Refer to Section 10.1 for a detailed description of the criteria used in the determination of sample size.

Withdrawals will not be replaced.

5.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (Day 361; T7) as described in the protocol.

Global completion of the study is required in order to provide enough subjects as defined in Section 10.1 Sample Size Determination.

6. STUDY POPULATION

6.1. Inclusion criteria for enrolment

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

Note: Prior to receipt of each vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects do not meet any of the applicable inclusion criteria listed below, they should not receive additional vaccinations.

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

- Subjects or/and subjects' parent(s)/Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the eDiaries, return for follow-up visits and is available for telephone calls).
- Written or witnessed/thumb printed informed consent obtained from the subject/parent(s)/LAR(s) of the subject prior to performance of any study specific procedure.
- Written informed assent obtained from the subject (if applicable) prior to performing any study specific procedure.
- A male or female between, and including, 10 and 25 years of age (i.e. 25 years + 364 days) at the time of the first vaccination.
- Healthy subjects as established by medical history physical examination and clinical judgment of the investigator before entering into the study.
- Subjects who are either unvaccinated with MenACWY vaccine or have received a single previous dose of MenACWY vaccine can participate in the study, if they have received it at least 4 years prior to informed consent and assent as applicable (with the exception of meningococcal C vaccination, if the last dose of MenC was received at ≤24 months of age).
- Female subjects of non-childbearing potential may be enrolled in the study. Please refer to Section 12.6.1 for definitions of menarche and menopause*.
- Female subjects of childbearing potential may be enrolled in the study, if the subject (refer to Section 12.6 and 12.6.1.1 for definitions of woman of child-bearing potential and adequate contraception):
  - 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 until 30 days after completion of Visit 6.

** A female is considered to be of non-childbearing potential prior to menarche and after natural or induced menopause. Natural menopause is recognised to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathological or physiological cause. Induced menopause is recognised to have occurred after hysterectomy, after bilateral oophorectomy, or iatrogenic ablation of ovarian function.*

6.2. Exclusion criteria for enrolment

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

Note: Prior to receipt of each study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects meet any of the applicable exclusion criteria listed below, they should not receive additional vaccinations. Eligibility to each study vaccination should be documented in the source documents.

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.

6.2.1. Medical conditions

- Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection within 60 days of enrolment.
- Progressive, unstable or uncontrolled clinical conditions.
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
- Any neuroinflammatory (including but not limited to: demyelinating disorders, encephalitis or myelitis of any origin), congenital neurological conditions, encephalopathies, seizures (including all subtypes such as: absence seizures, generalised tonic-clonic seizures, partial complex seizures, partial simple seizures). History of febrile convulsions should not lead to exclusion.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s)/product(s).
  - Hypersensitivity, including allergy, to any component of vaccines, including diphtheria toxoid (CRM $_{197}$) and latex medicinal products or medical equipment whose use is foreseen in this study.
- Abnormal function or modification of the immune system resulting from:
  - Autoimmune disorders (including, but not limited to: blood, endocrine, hepatic, muscular, nervous system or skin autoimmune disorders; lupus erythematosus and associated conditions; rheumatoid arthritis and associated conditions; scleroderma and associated disorders) or immunodeficiency syndromes (including, but not limited to: acquired immunodeficiency syndromes and primary immunodeficiency syndromes).
  - Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to study vaccination until the post-vaccination 3 blood sample (Visit 6). This will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.

- Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to study vaccination.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).

- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

6.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine(s)/product(s) during the period starting 30 days before the first dose of study vaccine(s)/product(s) (Day -29 to Day 1), or planned use during the study period.
- Previous vaccination against any group B meningococcal vaccine at any time prior to informed consent and assent as applicable.
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the first dose of study vaccine/ product or planned administration during the study period until the post-vaccination 3 blood sample (Visit 6).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the vaccine/product dose(s) until the post-vaccination 3 blood sample (Visit 6). For corticosteroids, this will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.

6.2.3. Prior/Concurrent clinical study experience

- 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 (drug or medical device).

6.2.4. Other exclusions

- Child in care

  Please refer to the glossary of terms for the definition of child in care.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- History of /current chronic alcohol abuse and/or drug abuse as determined by the investigator.
- Any study personnel or immediate dependants, family, or household member.

6.3. Criteria for temporary delay for enrolment and vaccination and/or blood sampling

(Amended 9 May 2021)

Enrolment/ vaccination/ blood sampling may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as body temperature ≥38.0°C (100.4°F). The preferred location for measuring temperature in this study will be the oral route.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.
- Significant acute illness within the previous 7 days.
- Receipt of systemic antibiotics within 3 days prior to blood sampling visit (Visit 1, Visit 2, Visit 4 and Visit 6) (this will defer the blood draw).
- A positive test for current infection with COVID-19. The testing should have been done using a molecular (polymerase chain reaction [PCR] or antigen test) approved by the country regulatory authorities.
- Subjects with known COVID-19 positive contacts in the past 14 days.
- Individuals who have received any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to and following each vaccination up to Visit 5*.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to the local governmental recommendations and ***that*** the Sponsor is ***notified accordingly***.

  In case of seasonal influenza vaccination, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations.

Under such circumstances, a subject may be considered eligible for study enrolment and vaccination and/or blood sampling after the appropriate window for delay has passed and inclusion/exclusion criteria have been re-checked, and if the subject is confirmed to be eligible.

6.4. Screen and baseline failures

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. Screen failures are subjects who withdraw or are withdrawn from the study following informed consent, but before randomisation to study treatment.

The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

7. TREATMENTS

Study treatment is defined as a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

7.1. Treatments administered

(Amended 9 May 2021)

Refer to the section on Study Supplies in the SPM for more details on storage and handling of the study vaccine(s)/product(s).

The study vaccines/ products specific to this study are described below.

- rMenB+OMV NZ (GSK's Meningococcal Group B Vaccine, *Bexsero*)***;***
- MenABCWY (GSK's combined investigational Meningococcal Groups A, B, C, W and Y Vaccine)***;***
- MenACWY (GSK's Meningococcal Groups A, C, W, and Y conjugate Vaccine, *Menveo*)***;***
- Placebo***.***

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

The vaccines are labelled and packed according to applicable regulatory requirements.

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

Table 9 Treatments administered

Study Treatment Name:	*Bexsero*	MenABCWY#		*Menveo****		Placebo
Vaccine(s)/Product(s) name	rMenB+OMV NZ	MenACWY lyo	rMenB+OMV NZ	MenA	MenCWY	NaCl
Presentation	Syringe	Vial	Syringe	Vial	Vial	Syringe
Dose form	Suspension for injection	Powder for suspension for injection	Suspension for injection	Powder for solution for injection	Solution for injection	Solution for injection
Vaccines/ product formulation†:	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHBP fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from N. meningitidis, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL	MenA(10 µg)-CRM_{197}; MenC(5 µg)-CRM_{197}; MenW135(5 µg)-CRM_{197}; MenY(5 µg)-CRM_{197}	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHBP fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from N. meningitidis, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL	MenA(10 µg)-CRM_{197} (16.7–33.3 µg)	MenC(5 µg)-CRM_{197} (7.1–12.5 µg); MenW135(5 µg)-CRM_{197}(3.3–8.3 µg); MenY(5 µg)-CRM_{197} (5.6–10 µg); water for injections q.s. 0.5 mL	Sodium chloride (NaCl) (0.9%); Water for injections
Route of Administration	Intramuscular use	Intramuscular use		Intramuscular use		Intramuscular use
Product category	***Combination***	***Combination***		***Biological***		***Combination***
Type	***Study; Control***	***Study***		***Control***		***Additional***
Administration site:						
Location	Deltoid	Deltoid		Deltoid		Deltoid
Laterality*	Non-dominant	Non-dominant		Non-dominant		Non-dominant
Number of doses to be administered:						
• MenB_0_2_6 group	3	-		1		-
• MenB_0_6 group	2	-		1		*1*
• ABCWY-1 group	-	2		-		*2*

Study Treatment Name:	*Bexsero*	MenABCWY#	*Menveo****	Placebo
• ABCWY-2 group • ABCWY-3 group • ACWY group	- - 2	2 2 -	- - 1	*2* *2* *1*
Volume to be administered**	0.5 mL	0.5 mL	0.5 mL	0.65 mL*****
Packaging and Labelling Do not include a sample of the label text or details of pack design in the protocol. It will be specified in the SPM	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK Biologicals SA	GSK Biologicals SA	GSK Biologicals SA	GSK Biologicals SA

OMV = Outer Membrane Vesicles; SPM = Study procedure manual; ***CRM 197 = Corynebacterium diphtheriae cross reacting material-197; fHbp = factor H binding protein; GSK = GlaxoSmithKline; NaCl = sodium chloride; NHBA = Neisserial heparin binding antigen; NZ = New Zealand***

† The composition per dose is presented here

***** 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.

** Refer to the SPM for the volume after reconstitution.

*** *Menveo* commercial formulation consisting of a MenA lyophilised component and of a MenCWY liquid component, to be reconstituted together before administration (0.5 mL) by a qualified healthcare professional. In the US, the approved specifications for Menveo are: MenA lyo: MenA=10 µg, CRM_{197}=12.5 µg - 33 µg; potassium dihydrogen phosphate; sucrose and MenCWY liquid: MenC=5 µg, CRM_{197} 6.25 µg –12.5 µg; MenW 135=5 µg, CRM_{197} 3.3 µg –10 µg; MenY=5 µg, CRM_{197} 3.3 µg– 10 µg; Sodium chloride; Sodium dihydrogen phosphate monohydrate; Disodium phosphate dihydrate; water for injections q.s. 0.5 mL.

MenABCWY formulation consisting of MenACWY lyo (lyophilised component) and of MenB liquid component, to be reconstituted together before administration (0.5 mL) by a qualified healthcare professional. Both the manufacture and the final composition of the MenB component of the MenABCWY are identical to that of the commercial *Bexsero*. However, to ensure a consistent reconstitution procedure and to reduce the risk of under-dosing the MenB component, the filling weight has been increased from a nominal 0.609 g presents in commercial *Bexsero* to 0.640g in the MenB component, used to reconstitute MenABCWY. Refer to SPM for details.

**** The volume of the saline pre-filled syringe may be between 0.6ml and 0.8 mL. The full volume is to be injected.

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Detailed vaccine preparation and administration instructions will be provided to investigators in the SPM prior to study start. The exact anatomic location of each injection must be carefully recorded in the Medical Chart and in the eCRF.

After completing the pre-vaccination procedures on Day 1, Day 61, Day 181 and Day 211, administer the vaccine to the subject. Observe the blinding procedures described in Section 7.3.

7.1.1. Precautions to be observed in administering study vaccine

Prior to each vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to each study vaccine administration is determined by evaluating the entry criteria outlined in protocol sections 6.1, Inclusion Criteria and 6.2, Exclusion Criteria and Section 7.7 regarding the contraindications to subsequent vaccination.

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine(s)/product(s) administration (Refer to Section 6.3), the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).

The subjects will be observed closely for at least 30 minutes following the administration of the vaccine(s)/product(s), with appropriate medical treatment readily available in case of anaphylaxis and/or syncope.

7.1.2. Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine rMenB+OMV NZ, MenABCWY and/or MenACWY.

An overdose would also occur if two doses of the study vaccine are administered within 2 weeks of the recommended interval between doses.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

7.2. Method of treatment assignment

There are 2 randomisation processes for each subject in the study.

- Randomisation to 1 of the 6 treatment groups (5:5:3:3:3:1 ratio). Refer to Section 7.2.2.
- Randomisation to strains for enc-hSBA testing (will be performed by the randomisation officer and a treatment blinded listing will be provided to GSK Laboratory or laboratory designated by GSK to schedule the enc-hSBA testing) (Refer Section 7.2.3)

7.2.1. 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. The Subject ID will be documented in the Screening and Enrolment log.

The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in Section 6 and evaluated during this screening procedure. The Subject ID will be the subject's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study.

7.2.2. Randomisation of treatment

7.2.2.1. Randomisation of supplies

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

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

7.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by component.

7.2.2.2.1. Study group and treatment number allocation

The target will be to enrol a total of 3651 eligible subjects who will be randomly assigned to 6 study groups in a 5:5:3:3:3:1 ratio (912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY group and 183 in ACWY group).

Allocation of the subject to a study group/a treatment number at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for study, region (US and ex-US countries), previous MenACWY vaccination (primed)? (Yes and No)*, and age category (10-17 years of age and 18-25 years of age). Minimisation factors will have equal weight in the minimisation algorithm.

To ensure adequate representation in the US in line with the post-marketing commitment (Section 3.1), a minimum of 30% of adolescents and young adults will be enrolled in the US.

After obtaining the signed and dated ICF/IAF from the subject/subject's parent/LAR and having checked the eligibility of the subject, blinded site staff will access SBIR. Upon providing the subject identification number, the subject's age category and previous MenACWY vaccination? (Yes/ No)*, the randomisation system will determine the study group and will provide the treatment number to be used for each dose. 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 SPM for specific instructions.

If for any reason, after randomisation the subject fails to undergo treatment, this is an early Termination and the reason should be recorded in source document as specified in the SDA.

Note that enrolment will be frozen as soon as the target numbers (Table 7) are reached. Refer to the SPM for further details.

Note: * Subjects with and without a previous MenACWY vaccination (primed and unprimed).

7.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine/product 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.

7.2.3. Allocation of subjects to assay subsets

Analysis of effectiveness and immunogenicity endpoints will be performed on different sub-sets of subjects, independent of allocation by study group. Refer to Section 10 for details. Blood samples will be collected from all subjects participating in the study.

7.2.3.1. Randomisation to strains for enc-hSBA testing

The evaluation of the randomly selected panel of invasive serogroup B strains (110 strains) for each vaccinated subject is not technically feasible with clinically acceptable blood volumes drawn from adolescents and young adults. For each applicable serum sample, 35 strains will be chosen completely at random from the 110 strains.

- The target number of strains to be tested for each subject will be 35 strains.
- The serum sample collected from each subject will be sent on an ongoing basis to GSK Clinical Laboratory Sciences or to laboratories delegated by GSK where the assays are available and qualified for the intended use. Aliquots for immunogenicity and enc-hSBA testing will be prepared depending on the serum volume available for a visit from one subject. A minimum amount of 5 mL of serum needs to be available to confirm eligibility to perform enc-hSBA testing. Additional instruction on the number of strains to be randomly assigned for enc-hSBA testing, according to the actual sample volume of serum provided to the laboratory, is provided in Section 10.1.2.

7.3. Blinding and unblinding

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine(s)/product(s) recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity, and effectiveness) will all be unaware of which vaccine/product was administered. To do so, vaccine/product preparation and administration will be done by qualified healthcare professional who will not participate in any of the study clinical evaluation. A minimum number of study site personnel responsible for preparing and / or delivering the injections will be unblinded. See Glossary of terms for definition of qualified healthcare professional and unblinded study staff. Site personnel responsible for delivering the injection must not be involved in study assessments. The study vaccine/placebo will be provided to the site as subjects' kits, similar in appearance, identified with treatment information (either Meningococcal Group B Vaccine or Meningococcal Groups A, B, C, W and Y Vaccine or Meningococcal Groups A, C, Y and W Conjugate Vaccine or placebo). Refer to SPM for details.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

The serological data, which could lead to the unblinding of the study groups, will not be available during the course of the study to any investigator or any person involved in the clinical conduct of the study or analysis.

7.3.1. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency when knowledge of the treatment is essential for the clinical

management or welfare of the subject.

The emergency unblinding process consists of the automated Internet-based system (SBIR) that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

As back-up process, the investigator has the option of contacting a GSK Helpdesk (refer to Table 10) if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Non-investigator physician (e.g. physician from emergency room) or subject/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back-up process). Contact details of investigator and GSK Helpdesk are reported in the patient/subject card.

Table 10 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Phone: +32 2 656 68 04 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

Refer to SPM for other country-specific numbers.

GSK Vaccines Clinical Safety and Pharmacovigilance (VCSP) staff may unblind the treatment assignment for any subject in case of Suspected Unexpected Serious Adverse Reaction (SUSAR) as well as in case of fatal or life-threatening cases. If the SAE requires an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4. Handling, storage and replacement of study vaccine(s)/product(s)

7.4.1. Storage and handling of study vaccine(s)/product(s)

The study vaccine(s)/product(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 authorised 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)/product(s).

A temperature excursion is any temperature that is not in range of the label storage temperature conditions. Temperatures outside the range of label storage temperature conditions must be reported and/or documented. Temperature excursion impacting study vaccine(s)/product(s) must be reported and/or documented.

In the frame of the reporting, the lack/absence of temperature monitoring documentation from a device meeting GSK requirements has to be considered as a temperature excursion.

Study vaccine(s)/product(s) 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).

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)/product(s).

7.4.2. Replacement of unusable vaccine(s)/product(s) doses

In addition to the vaccine/product doses provided for the planned number of subjects (including over-randomisation when applicable), at least 10% additional vaccine/product doses will be supplied to replace those that are unusable.

7.5. Concomitant medication(s)/product(s) and concomitant vaccinations

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

Concomitant medications include all medications taken by/administered to the subject at and after enrolment to treat any AE collected in the eCRF and any vaccine administered to subjects. These medication***s***/ vaccine***s*** must be documented on the Prior and Concomitant Medications and Vaccination eCRF.

At each study visit/contact, the investigator or delegate should question the subject and/or the subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject. When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in Section 6, Selection of Study Population to ensure that the subject should be enrolled/continue in the study.

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

- Any concomitant medications/products administered for treatment of an AE to be recorded as per the protocol-specified reporting period (see Table 14).

- Any concomitant vaccination administered in the period starting 14 days before the first dose of study vaccine(s)/product(s) and ending at the last study contact (Day -14 to Day 361).
- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the subject from the study (Refer to section 7.5.2 for further details).
- Any concomitant medications/products/vaccines relevant to an SAE/Adverse Event of Special interest (AESI) to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/AESI's. In addition, concomitant medications relevant to SAEs and AESI's need to be recorded on the expedited Adverse Event report.
- The use of antipyretic and/or other medications to prevent (prophylactic use) and/or treat fever during the first 7 days after vaccination to be recorded in the eCRF as well.

  Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present. An anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement]. The preferred location for measuring temperature in this study will be the oral route.
- The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications eCRF.
- The use of systemic antibiotics within 3 days prior to blood sampling visit is a reason to delay of blood sample withdrawal (see Section 6.3, Criteria for temporary Delay of Vaccination).
- The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.5.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 10.2 for populations to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s)/product(s) used during the study period.
- Investigational or non-registered medicinal products within 30 days prior to informed consent.
- Immunosuppressants or other immune-modifying drugs defined as follows:

  - Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent until the post-vaccination 3 blood sample (Visit 6).
  - Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
  - Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Immunoglobulins or any blood products at any dose and for any duration from 90 days prior to informed consent or until post vaccination 3 blood sample (Visit 6).

7.6. Intercurrent medical conditions that may lead to elimination of a subject from per-protocol analyses

If the subject meets one of the criteria mentioned in the Section 7.7, he/she may be eliminated from per protocol analysis.

7.7. Contraindications to subsequent vaccine(s) administration

Prior to receipt of additional study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination.

If subjects meet any of the original exclusion criteria or the criteria listed below, they should not receive additional vaccinations. However, the subjects should be encouraged to continue other study procedures at the discretion of the investigator (Section 8.5.7).

- Anaphylaxis following the administration of vaccines.
- Pregnancy (see Section 12.5.8.1).
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Any occurrence of an event listed in the exclusion criteria which must be always re-assessed by the investigator before administration of the next dose of study vaccine.
- Subjects who experience any serious adverse event judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Occurrence of a new AESI or the exacerbation of an existing AESI that, in the opinion of the investigator, exposes the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine(s)/product(s). Refer to Section 12.5.6 for the definition of AESIs.

7.8. Warnings and precautions

Warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to the Investigator Brochure for MenABCWY and the approved product label/package insert of rMenB+OMV NZ and MenACWY vaccines.

7.9. Treatment after completion of the study

During the study conclusion contact, the investigator will ask each subject/subject's parent(s)/LAR(s) if they are interested in participating/allowing the subject to participate in a booster study/long-term study. If a subject/subject's parent(s)/LAR(s) is/are not interested in participating in the booster study/long-term study the reason for refusal will be documented, when available, in the subject's CRF/eCRF.

The investigator is encouraged to share the immunological assay results for non-responders with the study subjects/subjects' parent(s)/LAR(s).

For the subjects identified as non-responders, it remains the responsibility of the investigator in charge of the subject's clinical management to determine the medical care needed as per local/regional practices (such as re-vaccination of the subject(s)).

Refer to Section 8.4.5 for details.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 2).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject(s) should discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations (i.e. eligibility criteria check) must be completed and results reviewed before confirming that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table 3.

8.1. 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.

During special circumstances, exemplified by the COVID-19 pandemic, certain study procedures may be adapted to protect the subject and promote data integrity. Refer to Section 8.9 for further details.

8.2. Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information.
- Medical history (any significant past diagnoses including allergies, hospitalisations, surgeries requiring in-patient hospitalisation, any other medical conditions which may impair the assessment of safety of the rMenB+OMV NZ, MenABCWY and MenACWY vaccines).
- Pre-vaccination body temperature.
- Post-vaccination immediate reactions observed for at least 30 minutes after injection (on Day 1, Day 61, Day 181 and Day 211): signs or symptoms of anaphylaxis, allergic phenomena (such as rashes, itching, or other allergic manifestations). Local and systemic solicited data (including e.g., use of medication to treat or prevent fever, and/or pain).Refer to Section 12.5.12.1 for details.
- Post-vaccination solicited local and systemic AEs collected at home by subject and/or subject's parent(s)/LAR(s) and recorded in the Subject eDiary for 7 days following each vaccination visit (at Day 1, Day 61 and Day 181). Any ongoing event (beyond 7 days) may be followed up for 30 days or until resolution, whichever is earlier, in the eDiary. Any solicited AE that has not resolved within 30 days post vaccination and is reported during clinic visits or safety follow-up calls will be entered into the subject's eCRF as an unsolicited AE. It will also be included in the subject's source documents at the site by the investigator/site staff as a verbally reported event. It will not be included in the Subject eDiary. These AEs will be analyzed as unsolicited AEs (i.e. in the Unsolicited Safety Set).
- Adverse Events.
  - Unsolicited AEs occurring within 30 days after each vaccination (at Day 1, Day 61 and Day 181) will be collected for all subjects by interviewing the subject and/or subject's parent(s)/LAR(s) (as applicable) during the site visits or Safety Follow-up Calls and by reviewing of available medical records.
  - SAEs occurring during the entire study period
  - Medically attended AEs occurring during the entire study period

  - AEs leading to premature withdrawal from the vaccination/study occurring during the entire study period
  - AESI occurring during the entire study period.
- Prior and concomitant medication as defined in Section 7.5.

All data collected must only be identified using the GSK Subject ID, as described in Section 7.2, documented in the source documents and entered in the eCRF*.

*Only the solicited local and systemic AEs 30 minutes post vaccination are entered in the eCRF. The solicited local and systemic AEs during 7-day post-vaccination period are not entered in the eCRF but are recorded in eDiary.

8.3. Pre-vaccination procedures

8.3.1. Screening/ Eligibility criteria

After an individual or individual's parent/LAR has consented participation in the study and informed consent/assent is signed, that individual will be given a unique Screening Number manually created by the investigator. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in Section 6 and evaluated during this screening procedure.

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

8.3.2. Collection of demographic data

Prior to study enrolment, demographic data will be collected from the subject, including date of birth (month and year), gender, race, ethnicity, weight, and height, and recorded in the subject's eCRF.

8.3.3. Medical history

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

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 study vaccination in the eCRF.

8.3.4. General and symptom-directed physical examination

A general physical examination is to be performed by a qualified healthcare practitioner. "Qualified health care practitioner" refers to any licensed or certified healthcare professional who is permitted by institutional policy to perform protocol required procedures, and who is identified within the Delegation of Responsibility Log. The physical examination will include examination of organ systems that are relevant to the investigator based on medical history and review of systems and a measurement of heart rate, blood pressure, and temperature.

These data will be written in the source document. Should the physical assessment reveal any abnormal values or events, these must be documented in the eCRF Adverse Events Form.

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

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 this examination should be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.3.5. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine(s)/product(s) may only be administered if the pregnancy test is negative.

Urine samples will be collected for pregnancy testing in females of child-bearing potential, before vaccinations at Visits 1, 3, 5 and 6, and the results recorded in the source document and the eCRF.

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

8.3.6. Pre-vaccination body temperature

The body temperature (preferably oral) of each subject needs to be measured prior to any study vaccines administration. If the subject has fever [fever is defined as body temperature ≥38.0°C/100.4°F regardless of the location of measurement] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Section 6.3).

Note: If the body temperature is measured by any other route (other than oral), this ***also*** needs to be recorded in the subject's eCRF.

8.4. Effectiveness and/or immunogenicity assessments

Please refer to the SPM and/or 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 the identification number for the subject (subject number).

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.

Future findings may make it desirable to use the samples acquired in this study for further research, not described in this protocol. Additional serological testing may be performed in the future to further characterise the antibody response to the antigens included in the study vaccines or hSBA against an additional panel of strains of *Neisseria* species.

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 further research. Further research will be subject to prior EC/IRB approval if required per local legislation.

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

Any sample testing will be done in line with the consent of the individual subject/subject's parent(s)/LAR(s)

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).

If additional testing is performed, the marker priority ranking given in Section 8.4.4 may be changed.

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.

8.4.1. Use of specified study materials

When materials are provided by GSK, 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 10.2 for the definition of populations for analyses). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK 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.

8.4.2. Biological samples

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

8.4.2.1. Blood sampling for effectiveness and immunogenicity response assessments

(Amended 9 May 2021)

A minimum of approximately 20 mL of blood will be drawn from all subjects at visit 1 before vaccination. ***A***pproximately ***30 mL sample of blood will be drawn from all subjects 30 days after the first and third vaccination [at Visit 2 (Day 31) and Visit 6 (Day 211)] and approximately*** 25 mL sample of blood will be drawn from all subjects 30 days after the second vaccination (at Visit 4 (Day 91)).

The blood samples should be collected before the study vaccination when applicable. The blood volume ***that is drawn as presented in Table 11*** is needed in order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and hSBA(s)). Refer to Section 5.1 and Section 7.2.3.1 for further details on the rationale for the requirement of this blood volume.

Check criteria for blood draw delay as specified in Section 6.3. A topical anaesthetic (e.g. EMLA adhesives or cream) may be used at the site of blood sample draw, according to local practice in order to minimise pain.

The blood will be processed as described in the SPM and/or Central Laboratory Manual. The serum will be stored at a temperature of -80°C (-70°C is accepted but -80°C is preferred). Each serum tube will be identified with a Central Laboratory label and sent to Central Laboratory per defined frequency. Complete instructions for labelling and storage of serum samples are included in the SPM and/or Central Laboratory Manual.

The total amount of blood collected over the study period per subject will be approximately ***105mL***.

Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements

Note: Blood samples are taken from all subjects irrespective of the testing status to maintain the blind of the study. Refer to Section 8.4 for details on how the unused/ left-over samples will be used.

Table 11 Biological samples

Sample type	Quantity	Unit	Timepoint	Subject/Group	Day
Blood	Approximately 20	mL	Visit 1 (Pre-Vacc)	All	Day 1
	Approximately ***30***	mL	Visit 2 (Post-Vacc 1)	All	Day 31
	Approximately 25	mL	Visit 4 (Post-Vacc 2)	All	Day 91
	Approximately ***30***	mL	Visit 6 (Post-Vacc 3)	All	Day 211
Note: in case of local regulations limiting the amount of blood to be taken in the younger population (e.g 10-12 years of age and/or at the lower bound of the percentile of the growth chart), a reduced amount of blood volume could be drawn at Visit 2 and Visit 6. In this population every effort must be done to collect at least 25ml of blood volume, samples will be analysed according to priority ranking provided in Table 13					

8.4.2.2. Other biological samples

- **Urine sampling**

Urine will be collected for pregnancy testing in females of child-bearing potential. Urine will be collected at Visit 1 before the first vaccination (Day 1), at Visit 3 before the second vaccination (Day 61), at Visit 5 before the third vaccination (Day 181) and at Visit 6 before vaccination (Day 211) and the results recorded in the source document and eCRF.

8.4.3. Laboratory assays

(Amended 9 May 2021)

Serum bactericidal activity is a functional measure of the ability of antibodies, in conjunction with human complement, to kill meningococci, and ***it*** is widely accepted as the serological surrogate marker for protection.

Effectiveness of the MenB component will be evaluated with serum bactericidal assays using endogenous source of human complement (enc-hSBA), on a panel of 110 US representative *N. meningitidis* serogroup B invasive disease strains.

Immunogenicity of the vaccine against serogroups A, B, C, W and Y will be evaluated by serum bactericidal assays using exogenous source of human complement (hSBAs), using indicator strains representing serogroups A, B, C, W and Y.

An Enzyme-Linked Immunosorbent Assay (ELISA), ***or equivalent,*** will be used to evaluate the serotype-specific IgG responses to A, C, W, and Y. The intent is to characterize whether the immunogenicity measured by hSBA using the MenA, C, W and Y indicator strains may be confounded by the contribution of the responses against the MenB antigens of the combination vaccine. The ELISA procedure is used to detect the amount of serum immunoglobulin G (IgG) antibodies in response to specific *N. meningitidis* polysaccharide antigens.

Effectiveness testing by enc-hSBA and MenACWY immunogenicity testing by hSBA will be prioritised over any other assays using exogenous source of human complement, or ELISA (***or equivalent)***, based on the volume of serum available for a visit from one subject.

Please refer to Section 12.2 for a detailed description of the assays performed in the study.

All testing will be performed at GSK Biologicals' laboratories or in a laboratory designated by GSK Biologicals (where the assays are available and qualified for the intended use) using standardised and validated procedures (refer to Section 12.2). Please refer to Section 12.3 for the address of the clinical laboratories used for sample analysis.

Table 12 Laboratory assays

System	*N meningitidis* Strains*	Method	Kit/Manufacturer	Unit	Laboratory
Serum	Panel of 110 strains [Welsch, 2018]	enc-hSBA	In-house	1/dilution	GSK laboratory** or laboratory designated by GSK
Serum	N men A (3125) Ab	hSBA	In house	1/dilution	
	N men C (C11) Ab				
	N men W (240070) Ab				
	N men Y (860800) Ab				
Serum	N men B fHbp (M14459) Ab	hSBA	In house	1/dilution	
	N men B NadA (96217) Ab				
	N men B PorA (NZ98/254) Ab				
	N men B NHBA (***M13520***) Ab				
Serum	N men A Ab IgG	ELISA#	TBD	µg/mL	
	N men C Ab IgG				
	N men W Ab IgG				
	N men Y Ab IgG				

Abbreviations: enc-hSBA: serum bactericidal assay with endogenous human complement; hSBA: serum bactericidal assay using human complement; 1/dilution: reciprocal of the dilution; IgG: Immunoglobin G; µg: Microgram, ELISA = enzyme-linked immunosorbent assay; N men: *Neisseria meningitidis*; TBD: to be determined.
* Strain(s) and/or assay cut-off(s) might be subject to change during the course of the study (e.g. in case of new qualification, (re-)validation or standardisation). In this case, this will be documented in the clinical report.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium ***or*** Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Siena, Italy or to an external laboratory
#For each of the MenACWY serogroups, ELISA ***(or equivalent*** assay***)*** cut-offs will be determined following validation of the assay. This will be documented in the clinical report.

Additional 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.

The GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

8.4.4. Biological samples evaluation

8.4.4.1. Immunological read-outs

(Amended 9 May 2021)

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 13.

Table 13 Immunological read-outs

Blood sampling time point		Group/ Subset name	No. subjects	Method[1]	Component	Components priority rank
Type of contact and time point	Sampling time point					
Visit 1 (Day 1)	Pre-Vacc 1	For details on number of subjects and groups/ subsets please refer to Section 10.1.2		hSBA	N men A (3125) Ab	1
				hSBA	N men C (C11) Ab	1
				hSBA	N men W (240070) Ab	1
				hSBA	N men Y (860800) Ab	1
				hSBA	N men B fHbp (M14459) Ab	2
				hSBA	N men B NHBA (***M13520***) Ab	2
				hSBA	N men B NadA (96217) Ab	2
				hSBA	N men B PorA (NZ98/254) Ab	2
Visit 2 (Day 31)	Post-Vacc 1			enc-hSBA	110 random US MenB strains	1
				hSBA	N men A (3125) Ab	2
				hSBA	N men C (C11) Ab	2
				hSBA	N men W (240070) Ab	2
				hSBA	N men Y (860800) Ab	2
				ELISA	N men A Ab IgG	3
				ELISA	N men C Ab IgG	3
				ELISA	N men W Ab IgG	3
				ELISA	N men Y Ab IgG	3
Visit 4 (Day 91)	Post-Vacc 2			enc-hSBA	110 random US MenB strains	1
				hSBA	N men B fHbp (M14459) Ab	2
				hSBA	N men B NHBA (***M13520***) Ab	2
				hSBA	N men B NadA (96217) Ab	2
				hSBA	N men B PorA (NZ98/254) Ab	2
Visit 6 (Day 211)	Post_vacc 3			enc-hSBA	110 random US MenB strains	1
				hSBA	***N men A (3125) Ab***	2
				hSBA	***N men C (C11) Ab***	2
				hSBA	***N men W (240070) Ab***	2
				hSBA	***N men Y (860800) Ab***	2
				hSBA	N men B fHbp (M14459) Ab	3
				hSBA	N men B NHBA (***M13520***) Ab	3
				hSBA	N men B NadA (96217) Ab	3
				hSBA	N men B PorA (NZ98/254) Ab	3
				ELISA	N men A Ab IgG	4
				ELISA	N men C Ab IgG	4
				ELISA	N men W Ab IgG	4
				ELISA	N men Y Ab IgG	4

Pre-Vacc: pre-vaccination; Post-Vacc: post-vaccination
[1] For detail regarding the method refer to Table 12.

8.4.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far against *N. meningitidis* serogroups A, B, W, and Y.

An hSBA titre ≥4 is a generally accepted correlate of protection against invasive meningococcal disease caused by *N. meningitidis* serogroup C.

The immunological assay results will be communicated to the investigator when ready and available.

8.5. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the study treatment or study.

8.5.1. Safety definitions

Please refer to Section 12.5 for safety definitions.

8.5.2. Follow-up Clinic Visit(s)

A follow-up clinic visit will be performed on Day 31 (-5/+14 days, Visit 2), Day 91 (-5 / +14 days, Visit 4) and Day 211 (-5 / +14 days, Visit 6).

The eDiary will be reviewed on Day 31 (Visit 2), Day 91 (Visit 4) and Day 211 (Visit 6).

Study-specific requirements are described in the SPM. For details on the eDiary see Section 12.5.9.

The subject and/or parent(s)/legal guardian(s) will be interviewed to determine if any unsolicited AEs occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit. The qualified healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are/were present. Adverse events reported by the subject and/or parent(s)/legal guardian(s) at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events CRF, as specified in Section 8.5, and not written on the script used for the interview.

Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication use. This assessment may include: measurement of vital signs, body temperature (preferably oral) and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in

accordance with their institutional policy. Clinically significant abnormalities should be reported as an AE in the CRF.

Blood sampling will be done as described in Section 8.4.2.1.

The site should schedule the next study visit/ study activity safety call with the subject and/or parent(s)/legal guardian(s) at each visit. The subject and/or parent(s)/LAR(s) will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalisation or an emergency room visit.

8.5.3. Safety Follow-up Calls

Safety follow-up phone calls are made on Day 15 (T1), Day 75 (T2), Day 121 (T3), Day 195 (T4), Day 241 (T5), Day 301 (T6), and Day 361 (T7). Safety follow-up calls are made to the subject by a qualified healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject and/or parent(s)/legal guardian(s) will be interviewed at Day 15 (SFU 1; T1), Day 75 (SFU 2; T2) and Day 195 (SFU 4; T4) according to the script, and information relating to any unsolicited AEs will be collected.

At all safety follow-up phone calls (T1 to T7) information relating to SAEs, AESIs, medically attended AEs and AEs leading to withdrawal will be collected. At all Safety Follow-up Calls concomitant medications associated with the AE and concomitant vaccinations have to be collected. All safety information described by the subject must be written down in a designated location within the source document. If this script is used as a source document, ensure that it meets the definition of a source document as per ICH GCP and/or local requirements.

The site should schedule the next study activity clinic (visit or safety call) with the subject and/or parent(s)/LAR(s).

The subject and/or parent(s)/legal guardian(s) will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalisation or an emergency room visit.

8.5.4. Time period and frequency for collecting AE and serious adverse event (SAE) information

An overview of the protocol-required reporting periods for AEs, SAEs, AESIs and pregnancies is given in Table 14. Refer to the Section 12.5.9.2 for details on the time period for recording safety information.

Table 14 Reporting periods for collecting safety information

Event	On V1*	V1 D1***	D7	V2 D31	V3 D61	D67	V4 D91	V5 D181	D 187	V6 D 211	D241	D301	*Study Conclusion* D 361
Solicited local and systemic AEs													
Unsolicited AEs													
AEs leading to withdrawal from the study													
Medically attended AEs**													
SAEs													
SAEs related to study participation or concurrent GSK medication/vaccine													

Event	On V1*	V1 D1***	D7	V2 D31	V3 D61	D67	V4 D91	V5 D181	D 187	V6 D 211	D241	D301	*Study Conclusion* D 361
AESIs													
Pregnancies													

.; V: Visit; D: Day, M: Month; T,Telephone call; COVID-19, Coronavirus Disease 2019
* i.e. consent obtained
** Including COVID-19 infection related AEs.
*** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration.

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Section 12.5. The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 14.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine(s)/product(s), the investigator will promptly notify the Study Contact for Reporting SAEs.

8.5.5. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5.9.

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subjects/subjects' parent(s)/LAR(s) is the preferred method to inquire about AE occurrence.

8.5.6. Reporting of serious adverse events, pregnancies, and other events

(Amended 9 May 2021)

Table 15 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK

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	***24 hours****	electronic pregnancy report	***24 hours****	electronic pregnancy report
AESIs	24 hours** ‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI
‡ The investigator will be required to confirm review of the SAE/AESI causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/AESI

8.5.6.1. Contact information for reporting of serious adverse events, AESIs and pregnancies

Table 16 Contact information for reporting of serious adverse events, AESIs and pregnancies

Study contact for questions regarding SAEs, AESIs and pregnancies
Refer to the local study contact information document
Back-up Study Contact for Reporting SAEs, AESIs and pregnancies
24/24 hour and 7/7 day availability: **GSK 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 US sites only: Fax: 1-610-787-7053 Canadian sites only: Fax: 1-866-903-4718

8.5.6.2. Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential for meeting legal obligations and ethical responsibilities for the safety of subjects and the safety of a study treatment under clinical investigation.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAE*s*) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.7. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE and non-serious AESIs (Refer Section 12.5.6 for definition), will be followed until the event is resolved, stabilised, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.5.12.4.

8.5.8. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE/ AESI should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.5).

8.5.9. Subject card

Study subjects/subjects' parent(s)/LAR(s) 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/subject's parent(s)/LAR(s). 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/subjects' parent(s)/LAR(s) must be instructed to keep subject cards in their possession at all times during the study duration.

8.5.10. Medical device deficiencies

(Amended 9 May 2021)

The study interventions (MenABCWY and Bexsero) are combination products constituted of a device and biologic product (e.g., pre-filled syringes). Refer to Glossary of terms for the definition of a combination product and a medical device deficiency.

8.5.10.1. Detection, follow-up and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 12.8 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or related of the device deficiency to the incident. Follow-up applies to all participants, including those who discontinue study intervention or the study.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

8.5.10.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to Section 12.8.2 for details of reporting.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.6. Holding rules and safety monitoring

There are no predetermined stopping rules other than circumstances for which subjects may not be eligible for additional study vaccinations or may be withdrawn from the study according to the best interests of the subject.

8.7. Biomarkers and pharmacogenomics

Biomarkers and pharmacogenomics are not evaluated in this study.

8.8. Study Termination Visit/ Study Conclusion

The study termination call will occur on Day 361. The termination visit will be a phone call (also in case of early termination of the study).

The date of termination is the date of the last contact (telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see Section 8.8.1.

During the phone call at the end of the study (Day 361), the following procedures will be performed: interview of subject and/or parent(s)/legal guardian(s) to collect SAEs, AESIs, medically attended AEs, pregnancies and/or concomitant medications/ vaccinations.

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject and/or parent(s)/legal guardian(s) chooses to share this information.

The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

8.8.1. Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomised but not treated.

At the clinic visit or during the telephone call, the following procedures will be performed:

- review of Subject eDiary (if applicable)
- interview of subject and/or parent(s)/legal guardian(s) to collect all AEs if termination occurs within 30 days after vaccination. If the termination occurs more than 30 days after the vaccination, all AEs within 30 days after vaccination and medically attended AEs, AEs leading to withdrawal, SAEs, pregnancy, AESIs beyond the 30 days after vaccination have to be collected.
- interview of subject and/or parent(s)/legal guardian(s) to collect concomitant medications administered to treat adverse events collected in the study,
- blood sampling (if withdrawal occurs at or prior to Visit 4 (Day 91) or Visit 6 (Day 211)) (if applicable)

The site will review with the subject and/or parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject and/or parent(s)/legal guardian(s) chooses to share this information.

The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

8.9. Study procedures during special circumstances

(Amended 9 May 2021)

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 subjects:

- If the Subject eDiary device was provided to the subject, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 6).
- Study visits may be performed at a different location* other than the study site (e.g. at subject's home). For study visits involving blood draw, biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 4), then the interval may be extended as described below in Table 17.
- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Table 4), then the interval may be extended as described below in Table 17.

  * It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site.

  In case of home visits, the study procedures should be carried out by a qualified person/s as delegated by the Principal Investigator, provided that the compliance with protocol procedures are ensured. Refer to Schedule of Activities for the schedule of visits (see Table 3).

  Refer to local regulations on the conduct of clinical trials during the COVID-19 pandemic for more details.

Impact on the per protocol set for immunogenicity will be determined on a case by case basis.

Table 17 Intervals between study visits during special circumstances

Interval	Length of interval	Allowed interval (Visit window)
Visit 1 → Visit 2	30 days	23 to ***58*** days after vaccination at V1 (from -7 to +***28*** days)
Visit 1→Visit 3	60 days	53 to ***88*** days after vaccination at V1 (from -7 to +***28*** days)
Visit 3→Visit 4	30 days	23 to ***58*** days after vaccination at V3 (from -7 to +***28*** days)
Visit 3→Visit 5	120 days	110 to 148 days after vaccination at V3 (from -10 to +28 days)
Visit 5→Visit 6	30 days	23 to ***58*** days after vaccination at V5 (from -7 to +***28*** days)

8.10. Decentralised study procedures

(Amended 9 May 2021)

If local regulations allow and if quality of study procedures can be maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals HCPs. Refer to the Schedule of Activities (Table 3) for the timing of these visits.

Following procedures can be performed remotely. Refer to the Glossary of terms for definitions of remote virtual visit:

- ***Biological samples may be collected remotely by qualified study staff/HCPs. Biological samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use.***
- ***Administration of study intervention can be performed remotely/at participant's home by qualified study staff/HCPs if appropriate storage conditions for the study intervention can be ensured. Furthermore, appropriate medical treatment must be readily available during 30 minutes after dosing in case of anaphylaxis, syncope.***

9. DISCONTINUATION FROM THE STUDY

From an analysis perspective, a 'withdrawal' from the study refers to any subject who was not available for the concluding contact foreseen in the protocol.

All data and samples 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 to contact those subjects who do not return for scheduled visits or follow-up.

Primary reason for study 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, by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Adverse events (AEs) requiring expedited reporting (please refer to section 12.5.10.2 for the details)
- Unsolicited non-serious AE
- Solicited AE
- Protocol deviation
- Withdrawal by subject, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- 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/pregnancy 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/pregnancy until resolution of the event (see Section 12.5.12).

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician (Refer to Section 7.3.1). The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE eCRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilisation.

Subjects who develop a SAE judged to be possibly or probably related to the study vaccine, including hypersensitivity reactions, should not receive subsequent vaccination.

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination eCRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject and/or parent(s)/legal guardian(s) can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject and/or parent(s)/legal guardian(s) intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

For sites in US: If a subject and/or parent(s)/legal guardian(s) withdraws consent but does not revoke the The Health Insurance Portability and Accountability Act (HIPAA) authorisation, the Sponsor will have full access to the subject's medical records, including termination visit information. If a subject and/or parent(s)/legal guardian(s) revokes only the HIPAA authorisation, the Sponsor will have full access to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up

Refer to Section 9.2.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination eCRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilisation.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the Study Termination eCRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardises the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorised deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by GSK and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study, despite the protocol requirement for adequate contraception, will not receive further vaccination but should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report eCRF (initial report) as soon as possible after learning of pregnancy occurrence (Refer to Section 12.5.9). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of follow-up period.

9.1. Discontinuation of study vaccine(s)/product(s)

A 'withdrawal' from the study vaccine(s)/product(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)/product(s) may continue further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

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

- Adverse event requiring expedited reporting
- Unsolicited non-serious adverse event (specify)
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

9.2. Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up. The termination date for the subject to be captured on the Study Termination eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

(Amended 9 May 2021)

Three thousand six hundred fifty-one (3,651) subjects are to be enrolled in the study. Figure 1 presents the study design overview with the breakdown of sample size per study arm:

- MenB_0_2_6: 912 subjects
- MenB_0_6: 912 subjects
- ABCWY-1: 548 subjects
- ABCWY-2: 548 subjects
- ABCWY-3: 548 subjects
- ACWY: 183 subjects.

It is assumed that 25% of the subjects will drop-out and not contribute to an evaluable result. The remaining subjects who do give an evaluable result provide 90% power to reject all hypotheses for the primary objectives of rMenB+OMV NZ and 92% power to reject all hypotheses for the primary objectives of MenABCWY vaccine. Additionally, the study is powered to reject key secondary objective for three *N. meningitidis* serogroup

B indicator strains (96217 (NadA), M14459 (fHbp), and ***M13520*** (NHBA)) with 81% power.

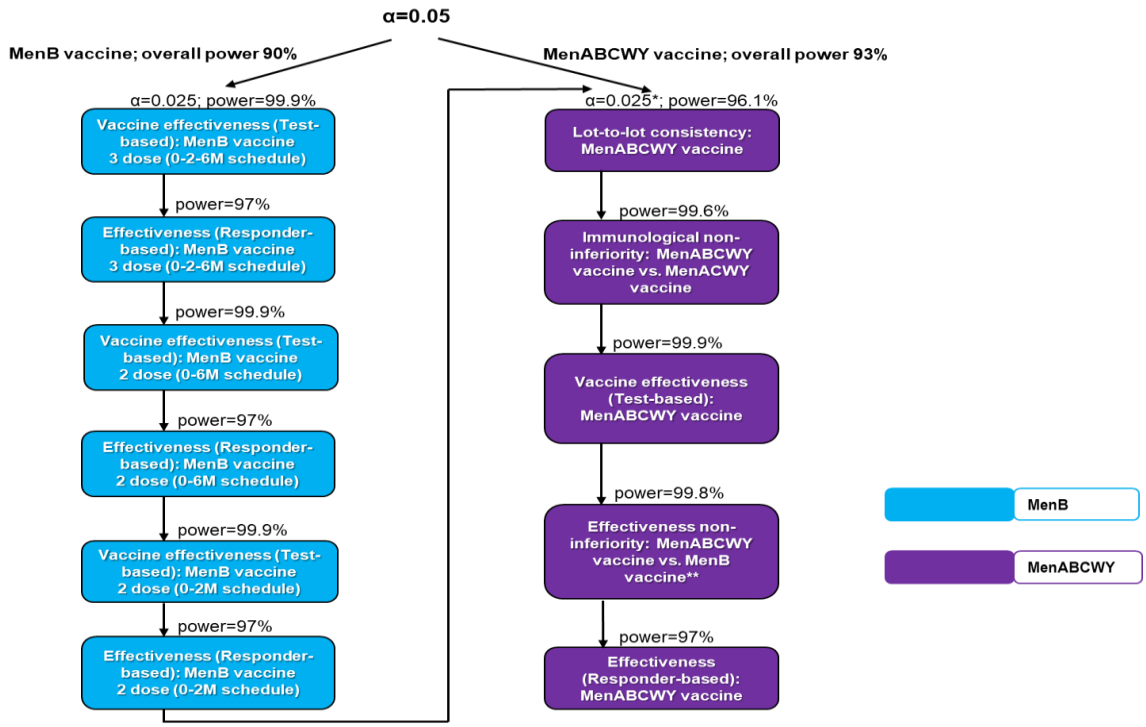
An explanation of the testing strategy and hypotheses can be found in Section 10.1.1 and its sub-sections. A breakdown of the power for the individual objectives can be found in Section 10.1.2 and its sub-sections.

10.1.1. Hypothesis testing strategy

Multiple objectives and endpoints require type I error control. Full alpha (0.05) is split equally (alpha=0.025) between rMenB+OMV NZ objectives and MenABCWY objectives. Furthermore, within rMenB+OMV NZ, as well as within MenABCWY, objectives are tested hierarchically. If the first null hypothesis is rejected, then the testing will continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis is not rejected, then the testing will stop.

As the comparator for MenABCWY non inferiority objective for the B component will be the selected schedule of rMenB+OMV NZ as determined in this study, the objectives of rMenB+OMV NZ will be analysed first. Additionally, if all null hypotheses related to rMenB+OMV NZ objectives will be rejected, the alpha (alpha=0.025) will be propagated to the MenABCWY part, and hypotheses related to MenABCWY objectives will be tested at full alpha (alpha=0.05). See Figure 2 for an explanation of the hierarchical testing (top to bottom, the order indicated by the arrows).

Figure 2 Hierarchical testing of hypothesis



* Alpha split equally between rMenB+OMV NZ and MenABCWY vaccine objectives.
If all rMenB+OMV NZ objectives achieved, MenABCWY vaccine objectives will be tested at full alpha.

** If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

An explanation of the hypothesis testing is given in the following subsections:

10.1.1.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

For demonstration of VE of rMenB+OMV NZ the following hypothesis will be tested:

Null hypothesis:

H_0: $VE \leq 65\%$

vs. Alternative hypothesis:

H_1: $VE > 65\%$

Where, VE represents the vaccine effectiveness, defined as 1- RR = (1- percentage of samples without bactericidal serum activity measured by enc-hSBA at a 1:4 dilution in the MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the ACWY group) x 100% and 65% is the pre-specified success criteria for VE. The VE against all 110 strains combined and associated 97.5% CI, will be computed by means of a generalised linear model. If the lower limit of the 97.5% CI for VE is > 65% effectiveness will be claimed.

10.1.1.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

A responder is defined as a subject with at least 70% of the strains killed in sera, one month after vaccination schedule.

Null hypothesis:

H_0: $\pi_B \leq 65\%$

vs.

Alternative hypothesis:

H_1: $\pi_B > 65\%$

Where π_B represents the percentages of responders observed at one month after vaccination schedule; and 65% is the pre-specified success criterion for the responder-

based endpoint. The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

10.1.1.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 10.1.1.1

10.1.1.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 10.1.1.2

10.1.1.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 10.1.1.1

10.1.1.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 10.1.1.2

10.1.1.7. Lot-to-lot consistency: MenABCWY - ACWY component

For demonstration of lot-to-lot consistency, the following equivalence hypotheses will be tested simultaneously for each of the 4 serogroups A, C, W, Y:

Null hypothesis:

H_0: $(\mu_{lot\ 1(i)} - \mu_{lot\ 2(i)}) \leq \log_{10}(0.5)$ *or* $(\mu_{lot\ 1(i)} - \mu_{lot\ 2(i)}) \geq \log_{10}(2)$ *or*

$(\mu_{lot\ 1(i)} - \mu_{lot\ 3(i)}) \leq \log_{10}(0.5)$ *or* $(\mu_{lot\ 1(i)} - \mu_{lot\ 3(i)}) \geq \log_{10}(2)$ *or*

$(\mu_{lot\ 2(i)} - \mu_{lot\ 3(i)}) \leq \log_{10}(0.5)$ *or* $(\mu_{lot\ 2(i)} - \mu_{lot\ 3(i)}) \geq \log_{10}(2)$

vs.

H_1: $(\mu_{lot\ 1(i)} - \mu_{lot\ 2(i)}) > \log_{10}(0.5)$ *and* $(\mu_{lot\ 1(i)} - \mu_{lot\ 2(i)}) < \log_{10}(2)$ *and*

$(\mu_{lot\ 1(i)} - \mu_{lot\ 3(i)}) > \log_{10}(0.5)$ *and* $(\mu_{lot\ 1(i)} - \mu_{lot\ 3(i)}) < \log_{10}(2)$ *and*

$(\mu_{lot\ 2(i)} - \mu_{lot\ 3(i)}) > \log_{10}(0.5)$ *and* $(\mu_{lot\ 2(i)} - \mu_{lot\ 3(i)}) < \log_{10}(2)$

Where $\mu_{lot\ 1(i)}$, $\mu_{lot\ 2(i)}$ and $\mu_{lot\ 3(i)}$ denote the means of log10-transformed titres for serogroups i=A, C, W and Y at 1 month after the second vaccination of the corresponding lot groups; and 0.5-2.0 are the non-inferiority margins for the ratio of GMTs between each pair of lots. Lot-to-lot consistency will be claimed if the two-sided 97.5% CIs for

the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.

10.1.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

For demonstration of non-inferiority of MenABCWY vs MenACWY in subjects without a previous MenACWY vaccination (unprimed), the following non-inferiority hypotheses will be tested simultaneously for each of the 4 serogroups A, C, W, and Y:

Null hypothesis:

$H_0: \pi_{ABCWY} - \pi_{ACWY} \leq -10\%$

vs.

Alternative hypothesis:

$H_1: \pi_{ABCWY} - \pi_{ACWY} > -10\%$

Where: π_{ABCWY} represents the percentages of subjects with a 4-fold rise 1 month after the last vaccination in the ABCWY group (pooled lots) and π_{ACWY} represents the percentage of subjects with a 4-fold rise 1 month after the first vaccination in the ACWY group; and -10% is the non-inferiority margin for the difference in between ABCWY group (pooled lots) and ACWY group. Immunological non inferiority of MenABCWY to MenACWY will be claimed if the LL of the 2-sided 97.5% CI for the group difference in percentages of subjects achieving a 4-fold rise in hSBA titres is above -10% for each serogroup.

10.1.1.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 10.1.1.1

10.1.1.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

For demonstration of non-inferiority of the VE of MenABCWY compared to the VE of rMenB+OMV NZ the following hypothesis will be tested:

Null hypothesis:

$H_0: \pi_{ABCWY} - \pi_{Control} \leq -5\%$

vs.

Alternative hypothesis:

$H_1: \pi_{ABCWY} - \pi_{Control} > -5\%$

Where: π_{ABCWY} and $\pi_{Control}$ represent the percentages of samples with bactericidal serum activity at 1:4 dilution in the ABCWY group (pooled lots) 1 month after the last MenABCWY vaccination and in the MenB group one month after the last rMenB+OMV NZ vaccination of the final schedule as determined in this study; and -5% is the non-inferiority margin for the difference in percentages of samples with bactericidal serum activity between ABCWY (pooled lots) and MenB group. Non inferiority of MenABCWY to rMenB+OMV NZ will be claimed if the LL of the 2-sided 97.5% CI for the group difference in percentages of samples with bactericidal serum activity at 1:4 dilution is above -5%.

10.1.1.11. Effectiveness (Responder-based): MenABCWY

See Section 10.1.1.2

10.1.2. Sample size justification

Overall study sample size and its power is provided in Section 10.1. This sub-section provides a breakdown of the power calculation for each of the objectives. All calculations are based on number of evaluable subjects.

10.1.2.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

The planned (target) number of strains to be tested for each subject will be 35 strains. A minimum amount of 5 mL of serum needs to be available to perform enc-hSBA testing. In case the volume of serum shipped to the laboratory for enc-hSBA testing is <5 mL, enc-hSBA testing will be still performed if the volume of serum allows to test a minimum number of 20 strains. Otherwise no enc-hSBA testing will be performed with the specific sample. The power was calculated for two situations: 30 and 35 strains to be tested per subject.

In study V102_16E1, the observed raw percentages of samples without bactericidal serum activity at 1:4 dilution were 77.8% in the MenACWY vaccine group and 21.9% in the MenABCWY group one-month post 3rd vaccination. The estimated VE of MenABCWY compared to MenACWY was 71% (95% CI: 69% - 73%). For the sample size calculations, it is assumed that MenB (any schedule) will have similar results as MenABCWY 0,2,6-months.

Table 18 shows the result of power calculation for a group size of 684 evaluable subjects in MenB group, (any schedule) and 137 subjects in MenACWY group. The percentage of tests without bactericidal serum activity for MenACWY is assumed to be 75%, while the estimation for MenB is 22%. Sample size calculations revealed >99.9% power to show that the lower limit of the two-sided 97.5% CI for the VE is >65% (Refer to Section 10.1.1.1)

Table 18 Power for VE 65% against all 110 strains combined, any schedule

% of tests without bactericidal serum activity at 1:4 dilution				Power	
MenACWY	MenB	Vaccine Effectiveness	Success Criterion (LL of 97.5% CI)	30 strains per subject	35 strains per subject
75%	20%	73%	>65%	99.9%	99.9%
77%	20%	74%	>65%	99.9%	99.9%
75%	22%	71%	>65%	99.9%	99.9%
77%	22%	71%	>65%	99.9%	99.9%
75%	25%	67%	>65%	84.4%	89.3%
77%	25%	68%	>65%	99.8%	99.9%

LL: lower level, CI: Confidence Interval, VE: Vaccine Effectiveness
* Computed by 10,000 simulation runs each based on SAS GENMOD procedure.

10.1.2.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Post-hoc calculations for study V102_16E1 were performed following a regulatory agency request. The calculated percentage of responders of subjects with >=70% of tested strains killed was 78.5% (95% CI [68.8%; 86.3%]) in the MenABCWY group one-month post 3rd vaccination. To have overall power of 90% (refer to Section 10.1), the effectiveness (responder-based) endpoint needs to have 97% power. Six hundred eighty-four (684) evaluable subjects will be necessary to demonstrate with at least 97% power that the lower limit of the 97.5% CI for proportion of responders in the MenB group (any schedule) is above 65% assuming the expected percentage in the study is 72.5% (see Table 19 below).

Table 19 Power for rMenB+OMV NZ Responder-based analysis 3 dose (0,2,6-months schedule)

N	% Responders – MenB	Success Criterion	Power
684	69%	65%	48.4%
684	72.5%	65%	97.6%
684	75%	65%	>99.9%

10.1.2.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

As the underlying assumptions for the rMenB+OMV NZ schedules are the same, see Section 10.1.2.1.

10.1.2.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

As the underlying assumptions for the rMenB+OMV NZ schedules are the same, see Section 10.1.2.2.

10.1.2.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

As the underlying assumptions for the rMenB+OMV NZ schedules are the same, see Section 10.1.2.1.

10.1.2.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

As the underlying assumptions for the rMenB+OMV NZ schedules are the same, see Section 10.1.2.2.

10.1.2.7. Lot-to-lot consistency: MenABCWY - ACWY component

One thousand two hundred thirty-three (1,233) evaluable subjects (411 evaluable subjects in each in ABCWY-1, ABCWY-2 and ABCWY-3 groups) are needed to demonstrate, for all pairs of lots, the two-sided 97.5% CIs for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5; 2.0] equivalence interval.

Assuming standard deviations as the 80% upper confidence limit of the ones observed in a previous GSK study with MenABCWY vaccine (V102_15) to account for possible more variation in new data, an assumed underlying ratio between lots of 1.2 and independency, a single equivalence test based on 411 evaluable subjects per lot group has power 99.0%->99.9% (see Table 20). The resulting overall power is 96.1%, because the total number of comparisons is 12 (three pairwise comparisons for the 4 serogroups A, C, W, and Y).

Table 20 Power calculation to demonstrate lot-to-lot consistency

Serogroup	SD	80% CI (UL)	Assumed underlying ratio	N	Power
A	0.5651582	0.616702951	1.2	411	99.7%
C	0.5048067	0.550847146	1.2	411	>99.9%
W	0.370505	0.404296579	1.2	411	> 99.9%
Y	0.627423	0.684646557	1.2	411	99.0%
Total (12 pairwise comparisons)					96.1%%

Note: SD – standard deviation; CI – confidence interval; UL – upper limit; N – number of evaluable subjects in each MenABCWY vaccine lot;

10.1.2.8. Immunological non-inferiority: MenABCWY vs. MenACWY *in subjects without a previous MenACWY vaccination (unprimed)*

Assuming at least 70% subjects without a previous MenACWY vaccination (unprimed), there will be at least 863 (70% out of 1233) evaluable subjects in the ABCWY group (pooled lots), at 1 month after the last vaccination, and 96 (70% out of 137) in the ACWY group at 1 month after the MenACWY vaccination (at Month 7 for ABCWY group (pooled lots) and at Month 1 for ACWY group). This sample size is sufficient to demonstrate that the lower limit of the two-sided 97.5% CIs for by percentage of subjects with 4-fold rise in hSBA titres against MenACWY indicator strains A, C, W and Y is > -10%.

Assuming similar underlying immune response after 2 doses of MenABCWY vaccine, as previously observed in study V102_16 (Column 2 and 3 of Table 21), the resulting overall power is 99.6%.

Table 21 Power calculation to demonstrate non-inferiority for serogroups A, C, W and Y of MenABCWY compared to MenACWY in subjects without a previous MenACWY vaccination (unprimed), at 1 month after the second dose vs 1 month after a single dose

Serogroup	MenABCWY % 4-fold rise (2 doses)	MenACWY % 4-fold rise (1 dose)	Power (%) for 70% unprimed subjects
A	92.4%	59.1%	>99.9%
C	95.4%	56.9%	>99.9%
W	80.4%	34.0%	>99.9%
Y	90.9%	62.8%	>99.9%
Total			99.6%

Unprimed = Subjects without a previous MenACWY vaccination

10.1.2.9. Vaccine effectiveness (Test-based): MenABCWY

As the underlying assumptions for MenABCWY 0-6M is the same as MenB, see Section 10.1.2.1.

10.1.2.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

The target number of evaluable subjects of 684 (in ABCWY group (pooled lots)) and 684 (in the Control group) at 1 month after the last vaccination is sufficient to demonstrate that the lower limit of the two-sided 97.5% CI for the difference in percentages of samples with bactericidal activity at 1:4 dilution in the ABCWY group (pooled lots) and in the Control group is above -5%.

Assuming the percentage of samples with bactericidal serum activity at 1:4 dilution in ABCWY group (pooled lots) 75% and 75%-78% in MenB, the power to show non-inferiority is ≥99.8%. (Table 22).

Table 22 Power calculation to demonstrate NI of MenABCWY to MenB

Percentages of killed samples MenABCWY 0-6M	Percentages of killed samples MenB	Expected Difference	N per group	Power
75%	75%	0%	684	> 99.9%
75%	76%	-1%	684	> 99.9%
75%	77%	-2%	684	> 99.9%
75%	78%	-3%	684	99.8%
75%	79%	-4%	684	64%

10.1.2.11. Effectiveness (Responder-based): MenABCWY

As the underlying assumptions for MenABCWY 0-6M is the same as MenB, see Section 10.1.2.2.

10.1.2.12. Non inferiority of MenABCWY vs rMenB+OMV NZ measured by percentage of subjects with 4-fold rise in hSBA titres against MenB component indicator strains post 2nd dose

(Amended 9 May 2021)

Key secondary objective is to demonstrate non inferiority of MenABCWY vs rMenB+OMV NZ measured by the percentages of subjects with 4-fold rise in hSBA titres against the *N. meningitidis* serogroup B indicator strains post 2nd dose. Six hundred twenty (620) subjects are needed to demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the MenB vaccination (0,2,6-months or 0,6-months or 0,2-months) with 81% power calculated for three strains (96217 (NadA), M14459 (fHbp), and ***M13520*** (NHBA)). NZ98/254 (PorA) is not powered for as the 4-fold rate for MenABCWY is predicted to be at least 10% less than the 4-fold rate for MenB.

Non-inferiority will be demonstrated if the LL of the 2-sided 97.5% CI for the group difference in percentage of subjects achieving a 4-fold rise in hSBA titres against all *N. meningitidis* serogroup B indicator strains is above -10%. Table 23 presents the power to meet the objective.

Table 23 Power of Non inferiority of MenABCWY vs rMenB+OMV NZ

Strain	4-fold rise (MenABCWY)	4-fold rise (rMenB+OMV NZ)	Power
96217 (NadA)	80%	80%	98.5%
M14459 (fHbp)	60%	60%	91.2%
M13520 (NHBA)	45%	45%	90.3%
NZ98/254 (PorA)	53%	76%	0%

10.2. Populations for analyses

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled Set	Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure. Refer to Glossary of terms for definition of an enrolled subject.
Exposed Set	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.
Full Analysis Set	All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data
Per Protocol Set	All subjects who received at least 1 dose of the study treatment to which they are randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.
Solicited Safety Set	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data
Unsolicited Safety Set	All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs

For analyses of the safety endpoints, subjects will be analysed "as treated" according to the actual vaccination a subject received. The list of protocol deviations that would result in exclusion from the PPS is available in Section 4.2.2.1 of the Statistical Analysis Plan.

Subgroups:

- Analyses of the primary objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex and US region**,** and subjects with and without a previous MenACWY vaccination (primed and unprimed) as relevant.
- Additional subgroup analyses may be performed to assess the impact of any COVID-19 pandemic. More details will be provided in the Statistical Analysis Plan if applicable.

10.3. Statistical analyses

10.3.1. Subjects disposition

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course) and completed will be described by group. Reason for early withdraw will be described by group. Full analysis and per-protocol analysis population set will be described by group.

10.3.2. Demography and baseline characteristics analyses

Descriptive statistics (mean, standard deviation (SD), median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

10.3.3. Primary effectiveness and immunogenicity analyses

Refer to Glossary of terms for definitions of test-based and responder-based vaccine effectiveness.

10.3.3.1. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: Per-protocol set (PPS) will be the primary analysis population

Statistical method: The VE is defined as 1- RR= (1- percentage of samples without bactericidal serum activity at 1:4 dilution in MenB group / percentage of samples without bactericidal serum activity at 1:4 dilution in the Control group) x100% and it will be analyzed using a generalised linear model with vaccine group, strain and centre as independent variables. Furthermore, a repeated statement will be used to estimate the variance of the RR including correlation within subject's responses. A centre effect will be tentatively included in the analysis; if the statistical model does not converge due to

the factor "centre", a model without centre effect will be fitted instead. The response variable of the model will be the Bernoulli distributed outcome without bactericidal activity at a 1:4 dilution (i.e. response is 1 if titre < 4, and 0 if titre ≥ 4), at 1 month after the last vaccination (Month 7) in the MenB group and at Month 1 for the ACWY group. Each subject will contribute with approximately 35 measures to this analysis, each of the measures corresponding to the response variable to one of the 35 strains randomly assigned to be tested with the samples available for that specific subject. For the statistical analysis it is assumed that the response to each strain is an independent measure with a unique true underlying rate and VEs are expected to vary among the strains. In order to obtain the VE measure which is a measure based on the relative risk (RR), a generalised linear model will be used with the Binary distribution and link function log in order to compute the log RR and the corresponding 97.5% CI. If this model would not converge, the Poisson distribution will be used instead. The obtained values will be exponentiated to obtain the RR and the corresponding 97.5% CI. The VE will be computed as 100% x (1 – RR). Effectiveness of rMenB+OMV NZ will be demonstrated if the lower limit of the two-sided 97.5% CI for VE against the selected strain panel between MenB and the ACWY group is above 65%.

10.3.3.2. Effectiveness (Responder-based): rMenB+OMV NZ - 3 doses (0,2,6-months schedule)

Analysis set: FAS will be the primary analysis population.

Statistical method: The percentage of responders (see definition in Section 10.1.1.2) and the corresponding exact two-sided 97.5% CI based on Clopper-Pearson method will be calculated [Clopper, 1934].

The objective is to demonstrate that the lower limit of the 97.5% CI for the percentage of responders is higher than 65%.

10.3.3.3. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 10.3.3.1

10.3.3.4. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,6-months schedule)

See Section 10.3.3.2

10.3.3.5. Vaccine effectiveness (Test-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 10.3.3.1

10.3.3.6. Effectiveness (Responder-based): rMenB+OMV NZ - 2 doses (0,2-months schedule)

See Section 10.3.3.2

10.3.3.7. Lot-to-lot consistency: MenABCWY - ACWY component

Analysis set: The analysis of lot-to-lot consistency will be based on the PPS.

Statistical method: For each of the three ABCWY lots (Lots 1, 2 and 3 of the MenACWY component of the ABCWY vaccine), GMTs and 97.5% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 97.5% CIs of the log transformed titres (base10) obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine lot and study centre. Additionally, lot-to-lot GMT ratios will be computed for each pair of ABCWY lots. Ninety-seven point five percent (97.5%) CIs for the ratios of GMTs will be constructed by exponentiating the difference of the least square means of the log transformed titres and the lower and upper limits of the 97.5% CIs on the difference obtained from the ANOVA model above.

Lot-to-lot consistency criterion: The three ABCWY lots will be considered equivalent if for each of the 4 serogroups A, C, W and Y and each pair of vaccine lots, the two-sided 97.5% CI on the ratio of GMTs at 1 month after the last vaccination will be contained within the interval [0.5, 2.0]

10.3.3.8. Immunological non-inferiority: MenABCWY vs. MenACWY in subjects without a previous MenACWY vaccination (unprimed)

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of subjects with 4-fold rise in hSBA titres against MenACWY indicator strains A, C, W and Y and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the ACWY group [Clopper, 1934]. The 97.5% CIs for the difference in percentages between ABCWY (pooled lots) and ACWY group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY (pooled) lots –ACWY) is above -10%.

10.3.3.9. Vaccine effectiveness (Test-based): MenABCWY

See Section 10.3.3.1

10.3.3.10. Effectiveness non-inferiority: MenABCWY vs. rMenB+OMV NZ

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution and the corresponding exact two-sided 97.5% CIs based on Clopper-Pearson method will be calculated for the ABCWY (pooled lots) group and the Men B group. The 97.5% CIs for the difference in percentages between ABCWY (pooled

lots) and MenB group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-Inferiority criterion: Non-inferiority of MenABCWY vaccine for the percentage of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution will be demonstrated if the lower limit of the two-sided 97.5% CI for the difference between the 2 groups (ABCWY (pooled) lots – MenB) is above -5%.

10.3.3.11. Effectiveness (Responder-based): MenABCWY

See Section 10.3.3.2

10.3.4. Secondary effectiveness and immunogenicity analyses

10.3.4.1. Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ

(Amended 9 May 2021)

Analysis set: PPS will be the primary analysis population.

Statistical method: The percentages of subjects with 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains (M14459, 96217, ***M13520*** and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

Non-inferiority criterion: Non-inferiority of MenABCWY vaccine for the proportion of subjects with 4-fold rise will be demonstrated if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with 4-fold rise between the 2 groups (ABCWY group (pooled lots) –selected MenB group) is above -10%.

10.3.4.2. Effectiveness by each of the endemic US *N. meningitidis* serogroup B strains

Analysis set: FAS effectiveness will be the primary analysis population. A subset (VE subset) of approximately 684 evaluable subjects per group, ABCWY (pooled lots) and of the MenB_0_2_6 or MenB_0_6 group would be used for the purpose of this analysis.

Statistical method: The VE per strain will be calculated as described in Section 10.3.3.1, using a generalised linear model with vaccine group, and centre as independent variables.

10.3.4.3. Distribution of percentages of serogroup B invasive disease strains killed

Analysis set: FAS effectiveness will be the primary analysis population. A subset (VE subset) of approximately 684 evaluable subjects per group, ABCWY (pooled lots) and of the MenB_0_2_6 or MenB_0_6 group would be used for the purpose of this analysis.

Statistical method: The distribution will be presented of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.

Summary statistics and 95% CI for the mean percentage will be presented, as well as a Figure of the cumulative distribution function.

10.3.4.4. Immune response of MenABCWY, rMenB+OMV NZ and MenACWY

(Amended 9 May 2021)

Analysis set: The analysis will be based on the FAS.

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each *N. meningitidis* serogroup A, C, W and Y and each B indicator strain (M14459, 96217, ***M13520*** and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be calculated with their associated 2-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be constructed by exponentiating the mean difference and the confidence limits in log10 (titre), using ANOVA with study centre included as an independent variable.

The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at baseline (Day 1, Month 0) and

- at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and
- at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1),

will be analyzed in a comparable way as described above for hSBA titres.

For each *N. meningitidis* A, C, W and Y and each serogroup B indicator strain (M14459, ***M13520***, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥ LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed.

10.3.5. Safety analyses

Distribution of subjects by vaccinations will be summarised by vaccine group for the Enrolled Set. In case of vaccination error, subjects will be analyzed "as treated" (according to the vaccine the subject actually received).

Analysis sets: Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events), Unsolicited Safety Set (unsolicited adverse events), and Overall Safety Set.

Endpoint	Statistical Analysis Methods
Primary	**Endpoints description**: The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. All solicited adverse events will be summarised according to defined severity grading scales, see protocol section 12.5.9.3 Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will be summarised for the intervals Day 1-3, Day 4-7, and Day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarised separately. The severity of solicited local adverse events, including redness (erythema) at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarised according to categories based on linear measurement: None (1 to 24mm); Mild (25 to 50mm); Moderate (51 to 100mm); Severe (>100mm). Injection site tenderness and systemic reactions (except fever) occurring up to 7 days after each vaccination at Day 1, Day 61 and Day 181 will be summarised according to "mild", "moderate" or "severe". Each solicited local and systemic adverse event will also be further summarised as "none" versus "any" (for fever the latter will be ≥38.0 °C). Use of antipyretics and analgesics will be summarised by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. Body temperature will be summarised by 0.5 °C increments from 36.0 °C up to ≥40 °C and will be broken down according by route of measurement, if applicable. Frequencies and percentages of subjects with temperatures ≥ 38.0 °C and temperatures ≥ 40.0 °C will also be presented.
	Endpoints description: The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 7 and the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period. This analysis applies to all adverse events occurring during the study, judged either as possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as possibly related to study vaccine, will be summarised according to system organ class and preferred term within system organ class. These summaries will be presented by vaccine group and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Endpoint	Statistical Analysis Methods
	Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data. Local and systemic AEs will be analyzed by point estimates with associated 95% CIs [Clopper, 1934].

10.3.6. Other analyses

Not applicable

10.3.7. Interim analyses

No interim analysis is planned for this study.

10.4. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations, glossary of terms and trademarks

12.1.1. List of abbreviations

(Amended 9 May 2021)

2019-nCoV:	2019 novel coronavirus disease
ABCs:	Active Bacterial Core Surveillance
ACIP:	Advisory Committee on Immunization Practices
ADE:	***Adverse Device Effect***
AE:	Adverse Event
CBER:	Center for Biologics Evaluation and Research, United States
CDC:	Centers for Disease Control and Prevention
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
COVID-19	Coronavirus disease 2019
CRM:	Cross-Reacting Material
CRO:	Contract Research Organisation
CT:	Computed tomography
DMC:	Data Monitoring Committee
EC:	Ethics Committee
ECDC:	European Center for Disease Prevention and Control
eCRF:	electronic Case Report Form
EDC:	Electronic Data Capture
EMA:	European Medicines Agency
EMLA:	Eutectic Mixture of Local Anesthetics
Enc-hSBA:	Endogenous complement human Serum Bactericidal Assay
EoS:	End of Study
FAS:	Full Analysis Set
FDA:	Food and Drug Administration, United States of America

fHbp:	factor H binding protein
GCP:	Good Clinical Practice
GSK:	GlaxoSmithKline
HIPAA:	The Health Insurance Portability and Accountability Act
hSBA:	Human Serum Bactericidal Assay
IAF:	Informed Assent Form
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
IEC:	Independent Ethics Committee
IM:	Intramuscular
IMD:	Invasive meningococcal disease
IND:	Investigational New Drug
IRB:	Institutional Review Board
LAR:	Legally Acceptable Representative
LLOQ:	Lower Limit of Quantitation
LOD:	Limit of Detection
LSLV:	Last Subject Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
MenACWY:	Meningococcal groups A, C, W-135 and Y Conjugate Vaccine
mL:	Milliliter
MLST:	MultiLocus Sequence Typing
NadA:	Neisseria adhesin A
NHBA:	Neisseria*l* Heparin Binding Antigen
NZ:	New Zealand
OMV:	Outer Membrane Vesicles
PCD:	Primary Completion Date
PO:	Per Os
PorA:	Porin A
PP:	Per protocol
PPS:	Per Protocol Set
RR:	Relative Risk

SADE:	***Serious Adverse Device Effect***
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SARI:	Severe Acute Respiratory Illness
SBA:	Serum Bactericidal Activity
SBIR:	Source data Base for Internet Randomization
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SoA:	Schedule of Activities
SOP:	Standard Operating Procedure
SPM:	Study Procedures Manual
SUSAR:	Suspected Unexpected Serious Adverse Reactions
T:	Telephone call
USADE	***Unanticipated Serious Adverse Device Effect***
VE:	Vaccine Effectiveness
VSAE:	Vaccines Serious Adverse Event
WHO:	World Health Organization

12.1.2. Glossary of terms

(Amended 9 May 2021)

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.
Adverse Event of Special Interest:	Adverse events of special interest (AESIs): are predefined (serious or non-serious) adverse events of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate, because such an event might warrant further investigation in order to characterise and understand it.
Blinding:	A procedure in which 1 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 observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 7.3 for details on observer-blinded studies).
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by

	foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Combination product:	***Combination product comprises any combination of*** • ***drug*** • ***device*** • ***biological product*** ***Each drug, device and biological product included in a combination product is a constituent part.***
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (T7). or Last testing results released of samples collected at Visit 6*. * In this case EoS must be achieved no later than 8 months after LSLV.
Enrolled	'Enrolled' means a subject's/parent's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to Section 10.2 for the definition of "Enrolled set" applicable to the study.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 10.2 for details on criteria for evaluability).
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/product: **(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.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Legally acceptable representative (The terms legal representative or legally authorised representative are used in some settings.)	An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Medically attended adverse events:	Symptoms or illnesses requiring hospitalisation, or emergency room visit, or visit to/by a health care provider.
Medical device deficiency:	***A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.***
Pharmacogenomics	The International Council on Harmonisation (ICH) E15 Guidance for Industry defines pharmacogenomics as Study of variation of DNA and RNA characteristics as related to drug or treatment response. Pharmacogenetics, which is a subset of pharmacogenomics, is “the study of variations in DNA sequence as related to drug response.” Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or

	effectiveness, mode of action). Proteomic and metabolomic biomarker research are not pharmacogenomics.
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.
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 Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK 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.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Protocol deviation:	A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardises the subject's health, safety, or rights.
Qualified healthcare professional:	Any licensed or certified healthcare professional who is permitted by institutional policy to perform protocol required procedures, and who is identified within the Delegation of Responsibilities Log.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Remote visit:	***Refers to the visit conducted in the place other than the study site.***
Responder-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of 110 meningococcus B US strains. Responder-based vaccine effectiveness is assessed based on the percentage of subjects considered responders, i.e., subjects whose serum kills the majority (≥70% in this study) of the tested strains following vaccination.

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 1 or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorised 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.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrolment.
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)/product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Test-based vaccine effectiveness:	The enc-hSBA methodology involves testing the serum samples from each individual subject against a subset of around 35 strains randomly chosen from the overall panel of

	110 meningococcus B US strains. Test-based vaccine effectiveness is assessed based on the overall percent of individual positive tests following vaccination and represents the reduction in risk compared to the placebo**.**
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 number identifying a treatment to a subject, according to treatment allocation.
Unblinded site staff:	Study personnel aware of the subject treatment allocation, delegated for administering study vaccines to subjects but not involved in the safety or immunogenicity evaluation of the subjects. All study vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for the specific study site.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

12.1.3. Trademarks

Trademark Information

Trademarks of the GSK group of companies	Generic description
Bexsero	Meningococcal group B vaccine (rMenB proteins + OMV NZ component, adsorbed on alum)
Menveo	Meningococcal Groups A, C, W-135 and Y Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine, MenACWY

12.2. Appendix 2: Clinical laboratory tests

The tests detailed in Table 12 will be performed at GSK or at a laboratory designated by GSK where the assays are available and qualified for the intended use.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6 of the protocol.

A urine pregnancy test will be conducted as needed for women of childbearing potential (refer to Section 8.3.5).

The investigator is not allowed to do extra testing on samples outside of what has been agreed upon by the ethic committees.

12.2.1. Effectiveness Assessment: Endogenous complement serum bactericidal assay – rMenB + OMV NZ

The measures of vaccine effectiveness against 110 invasive disease serogroup B strains will be based on the qualified endogenous complement serum bactericidal assay (enc-hSBA).

The qualified enc-hSBA assay provides a qualitative assessment (yes/no) of the presence of sufficient bactericidal antibodies in human sera to kill a meningococcal strain. In this study, test sera will be diluted 1:4 prior to testing. Serum samples will be collected using an appropriate process to preserve endogenous complement activity and to allow measurement of the bactericidal activity due to the antibodies present in the serum. This is in contrast to a traditional human serum bactericidal assay (hSBA) which heat inactivates the intrinsic complement proteins and uses an external source of human donor complement for each serum sample.

The enc-hSBA will be performed for each subject against a target number of 35 strains. A minimum amount of 5 mL of serum needs to be available to perform enc-hSBA testing. In case the volume of serum shipped to the laboratory for enc-hSBA testing is <5 mL, enc-hSBA testing will be still performed if the volume of serum allows to test a minimum number of 20 strains. Refer to Section 10.1.2.1 for details.

A given serogroup B meningococcal strain will be considered 'killed' for each sample positive for the enc-hSBA testing. Post-dose 1 sera from the ACWY group receiving the MenACWY vaccine will also be tested against serogroup B meningococcal strains by enc-hSBA (as a control).

12.2.2. MenB serum bactericidal assays using *exogenous* human complement (hSBA) – rMenB + OMV NZ

Serum bactericidal activity against rMenB+OMV NZ will be determined by using a validated manual (Tilt-based) hSBA against a standard panel consisting of 4 meningococcal B indicator strains M14459, 96217, NZ98/254 and ***M13520***. Each of these strains measures bactericidal activity primarily directed against one of the major bacterial antigens included in the vaccine: strain M14459 measures hSBA against the 741 part of the 936-741 antigen, also known as fHbp variant 1.1; strain 96217 measures hSBA against antigen 961c, also known as NadA; strain NZ98/254 measures hSBA against PorA P1.4, the immunodominant antigen in the OMV NZ vaccine component; strain ***M13520*** measures hSBA against the 287 part of the 287-953 antigen, also known as NHBA.

Serum bactericidal activity against rMenB+OMV NZ may be determined by performing serum bactericidal assays using human complement (hSBA) against an additional panel of Neisseria strains for exploratory objective if necessary.

12.2.3. MenACWY serum bactericidal assays using human complement (hSBA):

Serum bactericidal activity against MenACWY will be determined by using a validated agar-overlay hSBA.

This hSBA is based on the measurement of human complement-dependent bactericidal killing of meningococci. As with all functional hSBAs, the assay includes a first step of heat inactivation of the human serum samples to inactivate the endogenous complement, followed by serial dilution of the serum samples in which a fixed amount of bacteria and of human exogenous complement are added. The reactions are incubated to allow the association of meningococcal specific antibodies and their target antigen. The antibody-antigen complex activates the classical pathway of complement which ultimately results in bacterial lysis.

As a measure of the meningococcal specific antibody titre of each serum sample, the MenACWY agar-overlay hSBA follows the principle of detecting and counting the surviving meningococcal bacteria after bacterial growth within solid agar media, using an automatic colony counter (detection of colony forming units, CFU).

12.2.4. MenACWY IgG ELISA

The anti-MenACWY total IgG antibody (Ab) concentrations will be measured by using an Enzyme-Linked Immunosorbent Assay (ELISA), or equivalent, to evaluate the immunogenicity of the capsular polysaccharides of serogroups A, C, W and Y in MenACWY vaccine.

The assay characteristics (e.g. validated assay cut-offs and units) for each of the serogroup will be determined at the time of the generation of validation data.

Any change, including the change of the format of the assay, will be documented in a protocol amendment or in the clinical study report.

12.3. Appendix 3: Clinical laboratories

(Amended 9 May 2021)

Table 24 GSK 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 laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium ***or*** Wavre, Belgium CLS may delegate testing to GSK Research laboratories in Siena, Italy or to an external laboratory

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF) or Informed Assent Form (IAF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.

- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.4.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest prior initiation of the centre and for providing an update of Financial Disclosure if their financial interest changes at any point during their participation in a study and for 1 year after completion of the study.

12.4.3. Informed consent process

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

"Assent" is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained from the subject's parent(s) or legal guardian(s). Local laws define who constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a protocol [Levine, 1988].

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects/subjects' parent(s)/LAR(s) must be informed that their participation is voluntary.

Freely given and written or witnessed/thumb printed informed consent must be obtained from each subject and/or each subject's parent(s)/LAR(s) and subject informed assent, as appropriate, prior to participation in the study.

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

For subjects who become legally emancipated during the course of the study, e.g. become of the legal age of consent, re-consent is sought in accordance with local laws and regulations. The subject can provide consent by signing an ICF, similar to that provided to the parent(s)/LAR(s) at the study start, which summarises the study and includes a consent statement and documents that the subject agrees to continue participating in the study.

Subjects must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's parent(s)/LAR(s).

Subjects who are rescreened are required to sign a new ICF.

The study investigator is encouraged to obtain assent from the minor in addition to the consent provided by the LAR(s) when a minor is able to give assent to decisions about his/her participation in a study. The investigator is also accountable for determining a minor's capacity to assent to participation in a research study according to the local laws and regulations.

12.4.4. Data protection

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject's names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure the protection of personal data of investigator and the site staff which will be collected within the frame and for the purpose of the study.

12.4.5. Committees structure

12.4.5.1. Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 [ICH, 1997]. A signed and dated statement that the protocol and informed consent have been approved by the

IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained healthcare professionals who can perform all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any AE related to the study.
- If permission to do so is given by the subject and/or parent(s)/legal guardian(s), ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC

approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

i. to the IRB/IEC for review and approval/favourable opinion,

ii. to the Sponsor for agreement and, if required,

iii. to the regulatory authority(ies).

12.4.6. Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by GSK, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, GSK should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

12.4.7. Publication policy

GSK aims to publish the results of this study in searchable, peer reviewed scientific literature. GSK will target to submit within 18 months from LSLV for interventional studies and from the completion of the analysis for non-interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

12.4.8. Dissemination of clinical study data

The key design elements of this protocol will be posted on the GSK Clinical Study Register and on publicly accessible registers including ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases (e.g. EudraCT database) in compliance with the applicable regulations.

GSK also assures that results will be submitted to ClinicalTrials.gov within the required time-frame, in compliance with the current regulations mentioned in the table below.

At the time of study results posting, the full study protocol and statistical analysis plan will also be posted on ClinicalTrials.gov.

In addition, for studies that are in scope of the EU Clinical Trial Directive, summaries of the results of GSK interventional studies (phase I-IV) in paediatric/adult population will be posted within defined timelines on the publicly available EU Clinical Trial Register.

If it is not possible to submit a summary of the results within the required timelines 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.

	Clinicaltrial.gov	EU
Protocol summary	Before enrolment of subjects	As per CTA submission/Before enrolment of subjects
Results summary	Within 12 months of PCD (Primary and safety endpoint results)/Within 12 months of LSLV* (for secondary endpoint results)	Within 6 months (for paediatric population studies)/Within 12 months (for adult population studies) of EoS*.

* As defined in the study protocol.

Under the framework of the SHARE initiative, anonymised patient-level data from GSK sponsored interventional studies that evaluate products will be made available within 6 months of this publication to independent researchers whose research proposals have been approved by an independent panel. Requests for access may be made through www.clinicalstudydatarequest.com.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK 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.

12.4.9. Data quality assurance

(Amended 9 May 2021)

The investigator should maintain a record of the location(s) of their respective essential documents including source documents (see Glossary of terms for the exact definition of essential and source documents). The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial may be added or reduced where justified (in advance of trial initiation) based on the importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfil the requirements for certified copies (see Glossary of terms for the exact definition of certified copies).

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects see Glossary of terms for the exact definition of source documents) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data (see Glossary of terms for the exact definition of source data).

Study monitors will follow the Monitoring Plan to perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail). Safety and rights of subjects must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Quality tolerance limits (QTLs) will be pre-defined in the study management plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarised in the Clinical Study Report (CSR).

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.4.10. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and source documents can be found in the glossary of terms.

12.4.11. Study and site closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

Please refer to Section 8.8 for details.

12.5. Appendix 5: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

12.5.1. Definition of AE

12.5.1.1. AE Definition

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

NOTE: 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 study treatment.

12.5.1.2. Examples of events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine(s)/product(s) administration even though they may have been present prior to the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine(s)/product(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s)/product(s) administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits).

AEs to be recorded as endpoints (solicited AEs) are described in Section 12.5.3. All other AEs will be recorded as UNSOLICITED AEs.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

12.5.1.3. Examples of events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF**.**
- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.

12.5.2. Definition of SAE

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.

12.5.3. Solicited adverse events

a. Solicited local (injection-site) AEs

The following local (injection-site) AEs will be solicited:

Table 25 Solicited local adverse events

All age groups
Pain at injection site
Redness at injection site
Swelling at injection site
Induration at injection site

a. Solicited systemic AEs

The following systemic AEs will be solicited:

Table 26 Solicited systemic adverse events

Adult/Child (≥10 years)
Fatigue
Fever
Nausea
Headache
Arthralgia
Myalgia

Note: subjects/subjects' parent(s)/LAR(s) will be instructed to measure and record the oral body temperature in the evening, ideally at the same time each day. Should additional temperature measurements be performed at other times of day, subjects/subjects' parent(s)/LAR(s) will be instructed to record the highest temperature in the eDiary.

Note: If the body temperature is measured by any other route (other than oral), this also needs to be recorded in the subject's eCRF.

12.5.4. Other solicited adverse events

The use of analgesics/antipyretics for either prophylactic or treatment purposes will be recorded as other solicited events in the Subject eDiary and subsequently recorded onto the eCRFs and subject medical records.

The study staff must review the data entered into the Subject eDiary as described in Section 12.5.9.

12.5.5. Unsolicited adverse events

An unsolicited AE is an AE that was not solicited using an eDiary and that was spontaneously communicated by a subjects/parent(s)/LAR(s) who has signed the informed consent.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The subjects/ subject's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of subject/ parental /LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subject/subject's parent(s)/LAR(s) will be collected during interview with the

subjects/subject's parent(s)/LAR(s) and by review of available medical records at the next visit.

12.5.6. Adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) are predefined (serious or non-serious) adverse events of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate, because such an event might warrant further investigation in order to characterise and understand it.

12.5.6.1. Arthritis

Cases of arthritis are defined according to the following ad-hoc definition:

- Presence of a physical exam findings of swelling, redness, heat, or limitation in range of motion and/or
- Presence of a diagnostic imaging studies interpreted by a health care provider as demonstrating evidence of joint inflammation and/or arthrocentesis results evidencing inflammation.

Due to the heterogeneity of the presentation of arthritis which can be either acute or chronic, the threshold of duration of 6 weeks is to be considered.

The list of PTs corresponding to the diagnosis of arthritis, are those included in the MedDRA SMQ Narrow "Arthritis". For any new diagnosis of arthritis (serious or non-serious) in a study subject, the investigator (or designate) must complete, an electronic Expedited Adverse Events Report and an ad-hoc eCRF page on arthritis to further characterise this AESI.

12.5.6.2. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 27.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 27 List of potential immune-mediated diseases (pIMDs)

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: • Chronic inflammatory demyelinating polyneuropathy, • Multifocal motor neuropathy • Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: • Diffuse Scleroderma • CREST syndrome • Idiopathic inflammatory myopathies, including: • Dermatomyositis • Polymyositis • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: • Juvenile Idiopathic Arthritis • Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: • Ankylosing Spondylitis, • Reactive Arthritis (Reiter's Syndrome), • Undifferentiated Spondyloarthritis, • Psoriatic Arthritis, • Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localised Scleroderma (Morphoea).

Vasculitis	Blood disorders	Others
• Large vessels vasculitis including: • Giant Cell Arteritis (Temporal Arteritis), • Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: • Polyarteritis nodosa, • Kawasaki's disease, • Microscopic Polyangiitis, • Wegener's Granulomatosis (granulomatosis with polyangiitis), • Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), • Buerger's disease (thromboangiitis obliterans), • Necrotising vasculitis (cutaneous or systemic), • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), • Henoch-Schonlein purpura (IgA vasculitis), • Behcet's syndrome, • Leukocytoclastic vasculitis.	• Autoimmune haemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: • IgA nephropathy, • Glomerulonephritis rapidly progressive, • Membranous glomerulonephritis, • Membranoproliferative glomerulonephritis, • Mesangioproliferative glomerulonephritis. • Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: • Autoimmune uveitis • Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory Bowel disease, including: • Crohn's disease, • Ulcerative colitis, • Microscopic colitis, • Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type I. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as AESI. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as AESI until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of MedDRA preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

12.5.7. 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. x-ray imaging studies) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 12.5.1 and 12.5.2). 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or 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.

12.5.8. Events or outcomes not qualifying as adverse events or serious adverse events

12.5.8.1. Pregnancy

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

While pregnancy 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.

Note: The pregnancy 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 12.5.10.1 and 12.5.10.4:

- 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 recognised 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 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)/product(s) will be reported to GSK as described in Section 12.5.10. While the investigator is not obligated to actively seek this information from former subjects, he/she may learn of a pregnancy through spontaneous reporting.

12.5.9. Detecting and recording adverse events, serious adverse events and pregnancies

An Electronic Diary (eDiary) hereafter referred to as Subject eDiary will be used in this study to capture solicited local and systemic AEs. The subject or subject's parent/LAR should be trained on how and when to complete each field of the Subject eDiary.

The subjects/subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious or concerning.

Subject eDiary training should be directed at the individual(s) who will perform the measurements of AEs and who will enter the information into the Subject eDiary. This individual may not be the subject/subject's parent(s)/LAR(s), but if a person other than the subject/subject's parent(s)/LAR(s) enters information into the Subject eDiary, this person's identity must be documented in the subject's source document. Any individual that makes entries into the Subject eDiary must receive training on completion of the Subject eDiary at the time of the visit when Subject eDiary is dispensed. This training must be documented in the subject's source document.

Note: Subject eDiary can be filled in by a minor subject under the supervision of the subject's parent(s)/LAR(s) provided that the minor has the competency to assess and report the information to be provided in the diary card. The ultimate accountability for the completion of the Subject eDiary remains with the subject's parent(s)/LAR(s). The investigator should discuss this accountability with the subject's parent(s)/LAR(s).

Each subject/subject's parent(s)s/LAR(s) will be assigned a Subject eDiary at Visit 1 and shown how to use the device – this will include how to access the diary, performing test data entry on sample questions, and how to charge and store the device.

The subject/subject's parent(s)/LAR(s) will have to bring their completed eDiaries at Visit 2 and Visit 4, and return it at Visit 6. The returned Subject eDiaries should be verified during discussion with the subject/ subject's parent(s)/LAR(s) at these visits.

Note: If the Subject eDiary has been filled in by a minor subject, the investigator or delegate should verify the reported information during a discussion with the minor subject preferably in the presence of his/her parent(s)/LAR(s).

Any unreturned Subject eDiary will be sought from the subject/subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.

Refer to the SPM for more information regarding the use of eDiary.

Note: Any solicited AE that meets any of the following criteria must be entered into subjects' source document (see Section 12.5.9) and also as an AE on the Adverse Event eCRF:

- Solicited local or systemic AE that continues beyond day 7 after vaccination not captured in the eDiary.
- Solicited local or systemic AE that leads to a visit to a healthcare provider (medically attended AE, see Section 12.5.9.3.3).
- Solicited local or systemic AE leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (AE leading to withdrawal).
- Solicited local or systemic AE that otherwise meets the definition of an SAE (see Section 12.5.2) or an AESI (See Section 12.5.6).

Any new safety information reported during the safety follow-up phone call or site visits cannot be entered into the Subject eDiary. Such information must be described in the source documents as a verbally-reported event. Any adverse event reported in this fashion must be described as an unsolicited AE and therefore entered into the eCRF.

The investigator or delegate will transcribe the required information into the eCRF in English.

12.5.9.1. Post-vaccination reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject/subject's parent(s)/LAR(s) wishes to describe safety information, this information should only be collected by a qualified healthcare professional at the site, and the safety data described must be written down in the subject's medical chart.

Refer to SPM for details on Subject eDiary alerts.

12.5.9.2. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All solicited AEs during 7 days following administration of each dose of study vaccine(s)/product(s) (Day 1 to Day 7) (at Visit 1, Visit 3 and Visit 5) must be recorded in the eDiary, irrespective of intensity. Solicited local and systemic events that are ongoing after the 7-day reporting period may continue to be recorded in the eDiary until resolution or up to 30 days post-vaccination (ie, recording period for unsolicited AEs) whichever occurs first and do not need to be entered as an AE in the AE eCRF or the subject's source document. Any solicited AE that has not resolved within 30 days post vaccination and is reported during clinic visits or safety follow-up calls will be entered into the subject's eCRF as an unsolicited AE. It will also be included in the subject's source documents at the site by the investigator/site staff as a verbally reported event. It will not be included in the Subject eDiary. These AEs will be analysed as unsolicited AEs (i.e. in the Unsolicited Safety Set).

All other AEs during 30 days following administration of each dose of study vaccine(s)/product(s) (Day 1 to Day 30) (at Visit 1, Visit 3 and Visit 5) must be recorded in the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine(s)/product(s) and will end 6 months following administration of the study vaccines (Day 361 (T7) for each subject. See Section 12.5.10 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.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccines until study end.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccines and will end 6 months following administration of study vaccines (Day 361 (T7). See section 12.5.10 for instructions on reporting of pregnancies.

The time period for collecting and recording of AESIs will begin at the first receipt of study vaccines and will end 6 months following administration of the study vaccines (Day 361 (T7). See section 12.5.10.5 for instructions on reporting of AESIs.

12.5.9.3. Evaluation of adverse events and serious adverse events

12.5.9.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject or the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine(s)/product(s) or since the previous visit?*' (for subjects equal to and above 18 years of age)

OR

'*Has your child acted differently or felt different in any way since receiving the vaccine(s)/product(s) or since the last visit?*' (for subjects below 18 years of age)

When an AE/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 an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

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 AE/SAE and not the individual signs/symptoms.

12.5.9.3.2. Assessment of adverse events

Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 28 Intensity scales for solicited symptoms in adults and children of 10 years of age or more

Adults/Child (≥10 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Induration at injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F (with 1 decimal)
Nausea	0	Normal
	1	Mild: Nausea that is easily tolerated
	2	Moderate: Nausea that interferes with normal activity
	3	Severe: Nausea that prevents normal activity
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

*Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be oral

The maximum intensity of local Injection Site Induration, Swelling, Erythema (redness) will be scored at GSK as follows:

0 : 1 – 24 mm
1 : 25 - 50 mm
2 : 51 - 100 mm
3 : >100 mm

The maximum intensity of fever will be scored at GSK as follows:

0	:	< 38.0°C (100.4°F)
1	:	≥ 38.0 (100.4°F) - 38.9°C (102.1°F)
2	:	≥ 39.0 (102.2°F) - 39.9°C (103.9°F)
3	:	≥ 40.0°C (104.0°F)

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.

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice. In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in Section 12.5.2.

Assessment of causality

The investigator is obligated to assess the relationship between study vaccine(s)/product(s) and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE 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 AE 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)/product(s) will be considered and investigated. The investigator will also consult the IB and/or SmPC and/or 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. 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. 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.

All solicited local and systemic AEs will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the study vaccine/product?

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

If an event meets the criteria to be determined as 'serious' (see Section 12.5.2), 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)/product(s) (delete as applicable), if applicable.
- Erroneous administration.
- Other cause (specify).

Assessment of outcomes

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

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

12.5.9.3.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject/subject's parent(s)/LAR(s) will be asked if he/she/the subject received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF and source documents.

12.5.9.4. Recording of AEs related to COVID-19

For COVID-19 infection-related AEs, sites should follow routine AE/SAE processes as outlined in the protocol, using the following terms according to WHO defined case definitions:

- Suspected COVID-19 case
- Probable COVID-19 case
- Confirmed COVID-19 case [WHO, 2020]

12.5.9.4.1. WHO Case Definition

- Suspected COVID-19 case

  A. A person who meets the clinical AND epidemiological criteria

  Clinical criteria:

  Acute onset of fever AND cough OR acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status

  AND

  Epidemiological criteria:

  Residing or working in an area with high risk of transmission of virus: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; anytime within the 14 days prior to symptom onset OR residing to travel to an area with community transmission anytime within the 14 days prior to symptom onset OR working in any health care setting, including within health facilities or within the community; anytime within the 14 days prior to symptom onset

  OR

  B. A patient with severe acute respiratory illness (SARI: acute respiratory infection with history of fever or measured fever of ≥38.0°C, and cough; with onset within the last 10 days; and requires hospitalization)

- Probable COVID-19 case

  A. A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or epidemiologically linked to a cluster with at least one confirmed case

  OR

  B. A suspect case with chest imaging showing findings suggestive of COVID-19 disease*

  * Typical chest imaging findings suggestive of COVID-19 include the following:

  Chest radiography: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution

  Chest computed tomography (CT): multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution

  Lung ultrasound: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms

  OR

  C. A person with recent anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause.

  OR

  D. Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or epidemiologically linked to a cluster with at least one confirmed case.

- Confirmed COVID-19 case

  A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms. See “Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases” [WHO, 2019] for details.

12.5.10. Reporting of serious adverse events, pregnancies, and other events

12.5.10.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK

SAEs that occur in the time period defined in Section 12.5.9 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator becomes aware that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 12.5.9 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator becomes aware of the pregnancy.

AESIs that occur in the time period defined in Section 12.5.9 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a AESIs.

12.5.10.2. SAEs requiring expedited reporting to GSK

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.

12.5.10.3. 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 or email it to the Study Contact for Reporting SAEs (refer to the SPONSOR INFORMATION) or to GSK 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.

12.5.10.4. Completion and transmission of pregnancy reports to GSK

(Amended 9 May 2021)

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 ***24 HOURS***.

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.

12.5.10.5. Reporting of AESI's to GSK

Once an AESI is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is an AESI and whether it is serious or non-serious. The

report will always be completed as thoroughly as possible with all available details of the event, in accordance with the AESIs standard questionnaire provided. Even if the investigator does not have all information regarding an AESI, 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 AESI causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AESI.

Refer to Section 12.5.10.3 for back-up system in case the electronic reporting system does not work.

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

When additional SAE or 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 ***or emailed*** to the Study Contact for Reporting SAEs (refer to the SPONSOR INFORMATION) or to GSK Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

12.5.12. Follow-up of adverse events, serious adverse events, and pregnancies

12.5.12.1. Post-vaccination Procedures

Post-vaccination procedures will be performed on Day 1, Day 61, Day 181 and Day 211. After vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited AEs, and body temperature measurement. Record all safety data collected during this time in the eCRF for Day 1, Day 61 and Day 181.

Refer to Section 8.2 for details.

12.5.12.2. Post-vaccination Visit(s)

Post-vaccination visits or calls will be performed on Day 15, 75, 121, 195, 241, 301, and 361.

Refer to Sections 8.5.2 and 8.5.3 for details.

12.5.12.3. Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated AEs or interventions.

12.5.12.4. Follow-up of adverse events and serious adverse events

12.5.12.4.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK (within 24 hours for SAEs; refer to Table 15).

All SAEs and AESIs 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/contact of the subject.

All AEs 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/contact of the subject.

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

The investigator will follow subjects:

- With SAEs, AESIs (serious and non-serious) or subjects withdrawn from the study as a result of an AE, 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 using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK 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 AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

12.5.12.4.3. 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 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 6 to 8 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.

12.6. Appendix 6: Contraceptive guidance and collection of pregnancy information

12.6.1. Definitions

12.6.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

12.6.1.1.1. Women in the following categories are not considered WOCBP

- Premenarchal

  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).

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

12.6.2. Contraception guidance

- Female subjects of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in GSK list of highly effective contraceptive methods provided in Table 29.

Table 29 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] ***Failure rate of <1% per year when used consistently and correctly.***
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable • oral
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomised partner *(A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
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; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:
[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

12.6.3. Collection of pregnancy information

12.6.3.1. Female Subjects who become pregnant

(Amended 9 May 2021)

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within ***24 hours*** of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.5.10. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Please see section 12.5.9 , 12.5.10 and 12.5.12.4.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female subject who becomes pregnant while participating will discontinue study treatment.

12.7. Appendix 7: Genetics

Not applicable

12.8. Appendix 8: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

(Amended 9 May 2021)

12.8.1. Definition of medical device AE and adverse device effect (ADE)

- ***Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.***
- ***An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:***
  - ***insufficient or inadequate instructions for use (i.e. user error), or***
  - ***any malfunction of a medical device, or***
  - ***intentional misuse of the medical device.***

12.8.2. *Definition of medical device SAE, SADE and USADE*

A medical device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: – ***A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*** – ***A permanent impairment of a body structure or a body function.*** – ***Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.*** – ***Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function***
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
Serious Adverse Device Effect (SADE) definition
• ***A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.*** • ***Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate.***
Unanticipated SADE (USADE) definition
• ***An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.***

12.8.3. *Recording and reporting of medical device AE, ADEs, SADEs and USADE*

- ***Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.***
- ***E-mail/Facsimile transmission of the paper 'Medical device or combination product with device deficiency/incident report form' is the preferred method to transmit this information to the sponsor.***
- ***In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of 'Medical device or combination product***

with device deficiency/incident report form' sent by overnight mail or courier service.

- ***Contacts for reporting can be found in Section 8.5.6.1.***

GSK will review all device deficiencies, determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

12.9. Appendix 9: Country-specific requirements

None.

12.10. Appendix 9: Protocol Amendment/Administrative change History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date of Issue**
Protocol Amendment 4 Final	9 May 2021
Protocol Amendment 3 Final	23 September 2020
Protocol Amendment 2 Final	18 March 2020
Protocol Amendment 1 Final	23 May 2019
Protocol Final Version 1	29 January 2015

12.10.1. Protocol amendment 4

Overall Rationale for the Amendment change: The protocol is being amended to document the increase in blood volumes drawn at certain visits (Visit 2 and Visit 6) to improve the serum yield which is critical to evaluate the study endpoints. The allowed windows for study visits during special circumstances have also been widened to maintain subject visit compliance during the COVID-19 pandemic. Additionally, considering that some of the study interventions are combination products constituted of a device and biologic product (pre-filled syringes), the amended protocol provides instructions for collection of safety information related to the use of medical devices. The reporting period for pregnancies has also been updated in line with the current guidelines.

Table 2 List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Synopsis: Overall design Section 5.2: Overall design Section 8.4.2.1: Blood sampling for effectiveness and immunogenicity response assessments	The blood volume collected at Visit 2 and Visit 6 has been increased from 25mL to 30 mL.	This change has been made to increase serum yield which is critical to evaluate study endpoints.
Section 8.9: Study procedures during special circumstances	The allowed windows for study visits during special circumstances (Table 17) has been changed from +21 days to +28 days.	To allow for subject visit compliance during the global COVID-19 pandemic.
Section 7.1: Treatments administered Section 8.5.10: Medical device deficiencies Section 12.8: Appendix 8: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect	Product category and Type included Implementation of wording on medical device deficiency for combination products for Post Marketing Safety Reporting	In line with the FDA Combination Product Post Marketing Safety Reporting guidance.

Section # and Name	Description of Change	Brief Rationale
(SADE) and unanticipated SADE (USADE)		
Synopsis Table 1: Objectives and endpoints Section 4, Table 6: Objectives and endpoints Section 8.4.3: Laboratory assays Section 8.4.4.1: Immunological read-outs Section 10.1: Sample size determination Section 10.1.2.12: Non inferiority of MenABCWY vs rMenB+OMV NZ measured by percentage of subjects with 4-fold rise in hSBA titres against MenB component indicator strains post 2nd dose Section 10.3.4.1: Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ Section 10.3.4.4: Immune response of MenABCWY, rMenB+OMV NZ and MenACWY Section 12.2.2: MenB serum bactericidal assays using exogenous human complement (hSBA) – rMenB + OMV NZ	The NHBA strain has been changed from M07-0241084 to M13520.	The new strain has been approved for use in this study by competent authority.
Section 8.5.6: Reporting of serious adverse events, pregnancies and other events Section 12.5.10.4: Completion and transmission of pregnancy reports to GSK Section 12.6.3: Collection of pregnancy information	The timeframe for submitting pregnancy report to GSK is now 24 hours (changed from 2 weeks)	In line with the pregnancy reporting guidelines
Synopsis: Overall design Section 2: Schedule of activities Section 5.2: Overall design Section 8.10: Decentralised study procedures	Home/ remote visits (subject to allowance by local regulations and quality maintenance of study procedures) can be offered to subjects for the collection of biological samples and/or study intervention administration.	In alignment to the decentralised study procedures.
Section 8.4.3, Laboratory assays (Table 12) Section 12.3 Appendix 3 – Clinical laboratories	The laboratory at Marburg is removed from the list of GSK laboratories.	The laboratory at Marburg has become an external laboratory.

Detailed description of Protocol Amendment 4 changes:

The changed text of the amendment is indicated in bold italics in the body of the protocol. The deleted text (strikethrough) and the changed text (bold italics) are provided here below.

Cover page: Co-ordinating author(s)

PPD , Scientific Writer ~~and~~ PPD ~~, Scientific Writer for GSK~~

Cover page: Contributing authors

- PPD ~~and~~ PPD ~~Cont~~ Clinical Research and Development Lead~~s~~
- PPD ~~and~~ PPD - PPD , Oversight Data Managers
- PPD PPD , Clinical Laboratory Sciences Read-Out Team Lead
- PPD ~~and~~ PPD , Global Regulatory Affairs
- PPD PPD , Across Country Expert, Local Delivery Lead
- PPD and PPD PPD , Global Patents

In Protocol Amendment 4 Sponsor Signatory Approval:

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

In Synopsis (Synopsis Table 1) and Section 4 Objectives and Endpoints (Table 6):

Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month ~~18~~ ***12***].

N. meningitidis serogroup B indicator strains = M14459, 96217, ~~M07-0241084~~ ***M13520*** and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. ~~The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report~~.

In Synopsis Figure 1 and Section 5.2 Overall study design:

~~Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.~~

If local regulations allow and if quality of study procedures can be maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Refer to Section 8.10 (decentralised study procedures) for details

- Sampling schedule:
  - A total of 4 blood samples* will be collected from each subject at Day 1 (pre-vaccination blood sample; approximately 20 mL), at Day 31 (post-vaccination 1 blood sample; approximately ~~25~~ ***30*** mL), at Day 91 (post-vaccination 2 blood sample; approximately 25 mL) and at Day 211 (post-vaccination 3 blood sample; approximately ~~25~~ ***30*** mL).

In Section 2 Schedule of activities, under Table 3:

[9] ~~Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured. Refer to Section 8.9 for information related to study procedures during special circumstances~~

If local regulations allow and if quality of study procedures can be maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Refer to Section 8.10 (decentralised study procedures) for details.

[10] Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 12.5 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 14). In addition, separate COVID-19 specific eCRF form(s) should be completed. ***Refer to Section 8.9 for information related to study procedures during special circumstances***

In Section 2 Schedule of activities, under Table 4 Intervals between study visits:

Refer to Table 17 for intervals between study visits during special circumstances

In Section 3.2 Background:

The Meningococcal Group B Vaccine (Bexsero, rMenB+OMV NZ) contains three recombinant proteins [factor H binding protein (fHbp), Neisseria~~l~~ adhesin A (NadA), and Neisseria***l*** Heparin Binding Antigen (NHBA)], combined with Outer Membrane Vesicles (OMV) components from the New Zealand outbreak strain NZ98/254. rMenB+OMV NZ is immunogenic against the majority of circulating meningococcal serogroup B strains and has acceptable reactogenicity and safety profiles when administered to individuals across age groups.

In Section 5 Study design; Section 5.1 Scientific rationale for study design:

Rationale for blood volume collected:

In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA(s)), ***and ELISA (or equivalent), approximately 30 mL whole blood will be collected at Visit 2 and Visit 6 and approximately*** 25 mL whole blood will be collected at ~~Visit 2,~~ Visit 4 ~~and Visit 6~~. At pre-vaccination (Visit 1), 20 mL whole blood will be collected to provide the necessary serum volume for the hSBA ***and ELISA (or equivalent)***.

In Section 6.3 Criteria for temporary delay for enrolment and vaccination and/or blood sampling:

*In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to ~~its Prescribing Information and according to~~ the local governmental recommendations and ~~provided a written approval of~~ ***that*** the Sponsor is ~~obtained~~ ***notified accordingly.***

In Section 7.1, Treatments administered, under Table 7:

Study Treatment Name:	*Bexsero*	MenABCWY#	*Menveo****	Placebo
Product category	***Combination***	***Combination***	***Biological***	***Combination***
Type	***Study; Control***	***Study***	***Control***	***Additional***

OMV = Outer Membrane Vesicles; SPM = Study procedure manual; ***CRM 197 = Corynebacterium diphtheriae cross reacting material-197; fHbp = factor H binding protein; GSK = GlaxoSmithKline; NaCl = sodium chloride; NHBA = Neisserial heparin binding antigen; NZ = New Zealand***

In Section 8.4.2.1, Blood sampling for effectiveness and immunogenicity response assessments:

A minimum of approximately 20 mL of blood will be drawn from all subjects at visit 1 before vaccination~~, .and a~~***A***pproximately ***30 mL sample of blood will be drawn from all subjects 30 days after the first and third vaccination [at Visit 2 (Day 31) and Visit 6 (Day 211)] and approximately*** 25 mL sample of blood will be drawn from all subjects 30 days after the ~~first,~~ second ~~and third~~ vaccination (at ~~Visit 2 (Day 31),~~ Visit 4 (Day 91) ~~and Visit 6 (Day 211)~~).

The blood samples should be collected before the study vaccination when applicable. The blood volume ~~of 25 mL at Visit 2, Visit 4 and Visit 6~~ ***that is drawn as presented in Table 11*** is needed in order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and hSBA(s)). Refer to Section 5.1 and Section 7.2.3.1 for further details on the rationale for the requirement of this blood volume.

The total amount of blood collected over the study period per subject will be approximately ~~95~~ ***105***mL.

Table 11 Biological samples

Sample type	Quantity	Unit	Timepoint	Subject/Group	Day
Blood	Approximately 20	mL	Visit 1 (Pre-Vacc)	All	Day 1
	Approximately ~~25~~ ***30***	mL	Visit 2 (Post-Vacc 1)	All	Day 31
	Approximately 25	mL	Visit 4 (Post-Vacc 2)	All	Day 91
	Approximately ~~25~~ ***30***	mL	Visit 6 (Post-Vacc 3)	All	Day 211

Note: in case of local regulations limiting the amount of blood to be taken in the younger population (e.g 10-12 years of age and/or at the lower bound of the percentile of the growth chart), a reduced amount of blood volume could be drawn at Visit 2 and Visit 6. In this population every effort must be done to collect at least 25ml of blood volume, samples will be analysed according to priority ranking provided in Table 13

In Section 8.4.3 Laboratory assays

An Enzyme-Linked Immunosorbent Assay (ELISA), ***or equivalent,*** will be used to evaluate the serotype-specific IgG responses to A, C, W, and Y.

Effectiveness testing by enc-hSBA and MenACWY immunogenicity testing by hSBA will be prioritised over any other assays using exogenous source of human complement, or ELISA (***or equivalent)***, based on the volume of serum available for a visit from one subject.

Table 12 Laboratory assays

System	*N meningitidis* Strains*	Method	Kit/Manufacturer	Unit	Laboratory
Serum	N men B fHbp (M14459) Ab	hSBA	In house	1/dilution	
	N men B NadA (96217) Ab				
	N men B PorA (NZ98/254) Ab				
	N men B NHBA ~~(M07-0241084)*~~ ***(M13520)*** Ab				

** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium ~~or Marburg, Germany~~. CLS may delegate testing to GSK Research laboratories in Sienna, Italy or to an external laboratory
#For each of the MenACWY serogroups, ELISA ***(or equivalent*** assay***)*** cut-offs will be determined following validation of the assay. This will be documented in the clinical report

In Section 8.4.4.1 Immunological read-outs

Table 13 Immunological read-outs

Blood sampling time point		Group/ Subset name	No. subjects	Method[1]	Component	Components priority rank
Type of contact and time point	Sampling time point					
Visit 1 (Day 1)	Pre-Vacc 1	For details on number of subjects and groups/ subsets please refer to Section 10.1.2		hSBA	N men A (3125) Ab	1
				hSBA	N men C (C11) Ab	1
				hSBA	N men W (240070) Ab	1
				hSBA	N men Y (860800) Ab	1
				hSBA	N men B fHbp (M14459) Ab	2
				hSBA	N men B NHBA[2] ~~(M07-0241084)~~ ***(M13520)*** Ab	2

Blood sampling time point		Group/ Subset name	No. subjects	Method[1]	Component	Components priority rank
Type of contact and time point	Sampling time point					
				hSBA	N men B NadA (96217) Ab	2
				hSBA	N men B PorA (NZ98/254) Ab	2
Visit 2 (Day 31)	Post-Vacc 1			enc-hSBA	110 random US MenB strains	1
				hSBA	N men A (3125) Ab	2
				hSBA	N men C (C11) Ab	2
				hSBA	N men W (240070) Ab	2
				hSBA	N men Y (860800) Ab	2
				ELISA	N men A Ab IgG	3
				ELISA	N men C Ab IgG	3
				ELISA	N men W Ab IgG	3
				ELISA	N men Y Ab IgG	3
Visit 4 (Day 91)	Post-Vacc 2			enc-hSBA	110 random US MenB strains	1
				hSBA	N men B fHbp (M14459) Ab	2
				hSBA	N men B NHBA[2] ~~(M07-0241084)~~ ***(M13520)*** Ab	2
				hSBA	N men B NadA (96217) Ab	2
				hSBA	N men B PorA (NZ98/254) Ab	2
Visit 6 (Day 211)	Post_vacc 3			enc-hSBA	110 random US MenB strains	1
				hSBA	N men A ***(3125)*** Ab ~~IgG~~	2
				hSBA	N men C ***(C11)*** Ab ~~IgG~~	2
				hSBA	N men W ***(240070)*** Ab ~~IgG~~	2
				hSBA	N men Y ***(860800)*** Ab ~~IgG~~	2
				hSBA	N men B fHbp (M14459) Ab	3
				hSBA	N men B NHBA[2] ~~(M07-0241084)~~ ***(M13520)*** Ab	3
				hSBA	N men B NadA (96217) Ab	3
				hSBA	N men B PorA (NZ98/254) Ab	3
				ELISA	N men A Ab IgG	4
				ELISA	N men C Ab IgG	4
				ELISA	N men W Ab IgG	4
				ELISA	N men Y Ab IgG	4

[2] The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

In Section 8.5.6, Reporting of serious adverse events, pregnancies, and other events:

Table 15 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK

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~~ ***24 hours****	electronic pregnancy report	~~2 weeks~~ ***24 hours****	electronic pregnancy report

AESIs	24 hours** ‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI
‡ The investigator will be required to confirm review of the SAE/AESI causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/AESI

Section 8.5.10 was added:

8.5.10 Medical device deficiencies

The study interventions (MenABCWY and Bexsero) are combination products constituted of a device and biologic product (e.g., pre-filled syringes). Refer to Glossary of terms for the definition of a combination product and a medical device deficiency.

8.5.10.1 Detection, follow-up and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or related of the device deficiency to the incident. Follow-up applies to all participants, including those who discontinue study intervention or the study.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

8.5.10.2 Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to Section 12.8.2 for details of reporting.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

In Section 8.9 Study procedures during special circumstances:

Table 17 Intervals between study visits during special circumstances

Interval	Length of interval	Allowed interval (Visit window)
Visit 1 → Visit 2	30 days	23 to ~~51~~ ***58*** days after vaccination at V1 (from -7 to +~~21~~ ***28*** days)
Visit 1→Visit 3	60 days	53 to ~~81~~ ***88*** days after vaccination at V1 (from -7 to +~~21~~ ***28*** days)
Visit 3→Visit 4	30 days	23 to ~~51~~ ***58*** days after vaccination at V3 (from -7 to +~~21~~ ***28*** days)
Visit 3→Visit 5	120 days	110 to 148 days after vaccination at V3 (from -10 to +28 days)
Visit 5→Visit 6	30 days	23 to ~~51~~ ***58*** days after vaccination at V5 (from -7 to +~~21~~ ***28*** days)

Section 8.10 has been added:

8.10 Decentralised study procedures

If local regulations allow and if quality of study procedures can be maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals HCPs. Refer to the Schedule of Activities (Table 3) for the timing of these visits.

Following procedures can be performed remotely. Refer to the Glossary of terms for definitions of remote virtual visit:

- ***Biological samples may be collected remotely by qualified study staff/HCPs. Biological samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use.***
- ***Administration of study intervention can be performed remotely/at participant's home by qualified study staff/HCPs if appropriate storage conditions for the study intervention can be ensured. Furthermore, appropriate medical treatment must be readily available during 30 minutes after dosing in case of anaphylaxis, syncope.***

In Section 10.1, Sample size determination:

It is assumed that 25% of the subjects will drop-out and not contribute to an evaluable result. The remaining subjects who do give an evaluable result provide 90% power to reject all hypotheses for the primary objectives of rMenB+OMV NZ and 92% power to reject all hypotheses for the primary objectives of MenABCWY vaccine. Additionally, the study is powered to reject key secondary objective for three *N. meningitidis* serogroup B indicator strains (96217 (NadA), M14459 (fHbp), and ~~M07-0241084~~ ***M13520*** (NHBA~~*~~)) with 81% power.

~~* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.~~

In Section 10.1.2.12, Non inferiority of MenABCWY vs rMenB+OMV NZ measured by percentage of subjects with 4-fold rise in hSBA titres against MenB component indicator strains post 2nd dose:

Key secondary objective is to demonstrate non inferiority of MenABCWY vs rMenB+OMV NZ measured by the percentages of subjects with 4-fold rise in hSBA titres against the *N. meningitidis* serogroup B indicator strains post 2nd dose. Six hundred twenty (620) subjects are needed to demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the MenB vaccination (0,2,6-months or 0,6-months or 0,2-months) with 81% power calculated for three strains (96217 (NadA), M14459 (fHbp), and ~~M07-0241084~~ ***M13520*** (NHBA~~*~~)). NZ98/254 (PorA) is not powered for as the 4-fold rate for MenABCWY is predicted to be at least 10% less than the 4-fold rate for MenB.

~~*The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.~~

Table 23 Power of Non inferiority of MenABCWY vs rMenB+OMV NZ

Strain	4-fold rise (MenABCWY)	4-fold rise (rMenB+OMV NZ)	Power
96217 (NadA)	80%	80%	98.5%
M14459 (fHbp)	60%	60%	91.2%
~~M07-0241084~~-***M13520*** (NHBA)	45%	45%	90.3%
NZ98/254 (PorA)	53%	76%	0%

In Section 10.3.4.1, Immunological non-inferiority: MenABCWY vs. rMenB+OMV NZ:

Statistical method: The percentages of subjects with 4-fold rise in hSBA titres against *N. meningitidis* serogroup B indicator strains (M14459, 96217, ~~M07-0241084*~~ ***M13520*** and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively) at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) and 1 month after the 3-dose vaccination series (Day 211, Month 7) in MenB_0_2_6 group or 2-dose vaccination series (Day 211, Month 7) in MenB_0_6 group or 2-dose vaccination series (Day 91, Month 3) in MenB_0_2_6 group and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated [Clopper, 1934]. The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and MenB_0_2_6 group and MenB_0_6 group will be constructed using the method of Miettinen and Nurminen [Miettinen, 1985].

~~* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.~~

In Section 10.3.4.4, Immune response of MenABCWY, rMenB+OMV NZ and MenACWY:

Statistical method: The hSBA titres at each time point for all groups (ABCWY group (pooled lots), MenB_0_2_6 and MenB_0_6 groups) will be logarithmically transformed (base10) to fulfil the normal distribution assumption. For each *N. meningitidis* serogroup A, C, W and Y and each B indicator strain (M14459, 96217, ~~M07-0241084*~~ ***M13520*** and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively), the GMTs and GMRs (post-vaccination/baseline) will be calculated with their associated 2-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. The ratio of GMTs and GMRs between two groups and the corresponding CI will be constructed by exponentiating the mean difference and the confidence limits in log10 (titre), using ANOVA with study centre included as an independent variable.

For each *N. meningitidis* A, C, W and Y and each serogroup B indicator strain (M14459, ~~M07-0241084~~* ***M13520***, 96217and NZ98/254) the percentages of subjects with hSBA titres ≥ LLOQ and of subjects with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint not previously analyzed.

**** The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.***

In Section 12.1.1, Abbreviations:

ADE:	***Adverse Device Effect***
NadA:	Neisseria~~l~~ adhesin A
NHBA:	Neisseria***l*** Heparin Binding Antigen
SADE:	***Serious Adverse Device Effect***
USADE	***Unanticipated Serious Adverse Device Effect***

In Section 12.1.2, Glossary of terms:

Combination product:	***Combination product comprises any combination of*** • ***drug*** • ***device*** • ***biological product*** ***Each drug, device and biological product included in a combination product is a constituent part.***
Medical device deficiency:	***A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.***

Remote visit: ***Refers to the visit conducted in the place other than the study site.***

In Section 12.2.2, MenB serum bactericidal assays using *exogenous* human complement (hSBA) – rMenB + OMV NZ:

Serum bactericidal activity against rMenB+OMV NZ will be determined by using a validated manual (Tilt-based) hSBA against a standard panel consisting of 4 meningococcal B indicator strains M14459, 96217, NZ98/254 and ~~M07-0241084~~ ***M13520***. Each of these strains measures bactericidal activity primarily directed against one of the major bacterial antigens included in the vaccine: strain M14459 measures hSBA against the 741 part of the 936-741 antigen, also known as fHbp variant 1.1; strain 96217 measures hSBA against antigen 961c, also known as NadA; strain NZ98/254 measures hSBA against PorA P1.4, the immunodominant antigen in the OMV NZ vaccine component; strain ~~M07-0241084~~ ***M13520*** measures hSBA against the 287 part of the 287-953 antigen, also known as NHBA.

~~The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.~~

In Section 12.3, Clinical laboratories:

Table 24 GSK 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~~

* GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium ***or*** Wavre, Belgium ~~or Marburg, Germany~~. CLS may delegate testing to GSK Research laboratories in Sienna, Italy or to an external laboratory

In Section 12.4.9, Data quality assurance:

Quality tolerance limits (QTLs) will be pre-defined in the study management plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarised in the Clinical Study Report (CSR).

In Section 12.5.10.4, Completion and transmission of pregnancy reports to GSK:

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 ~~2WEEKS~~ ***24 HOURS***.

In Section 12.6.3.1, Female Subjects who become pregnant:

Information will be recorded on the appropriate form and submitted to GSK within ~~2 weeks~~ ***24 hours*** of learning of a subject's pregnancy.

Section 12.8, Appendix 8 has been added:

12.8 Appendix 8: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

12.8.1 Definition of medical device AE and adverse device effect (ADE)

- ***Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.***

- ***An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:***

  - ***insufficient or inadequate instructions for use (i.e. user error), or***

  - ***any malfunction of a medical device, or***

  - ***intentional misuse of the medical device.***

12.8.2 Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
e. Led to death
f. Led to serious deterioration in the health of the participant, that either resulted in: • ***A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*** • ***A permanent impairment of a body structure or a body function.*** • ***Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.*** • ***Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function***
g. Led to fetal distress, fetal death or a congenital abnormality or birth defect

h. Is a suspected transmission of any infectious agent via a medicinal product
Serious Adverse Device Effect (SADE) definition
• ***A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.*** • ***Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate.***
Unanticipated SADE (USADE) definition
• ***An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.***

12.8.3 Recording and reporting of medical device AE, ADEs, SADEs and USADE

- ***Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.***
- ***E-mail/Facsimile transmission of the paper 'Medical device or combination product with device deficiency/incident report form' is the preferred method to transmit this information to the sponsor.***
- ***In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of 'Medical device or combination product with device deficiency/incident report form' sent by overnight mail or courier service.***
- ***Contacts for reporting can be found in Section 8.5.6.1.***

GSK will review all device deficiencies, determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

12.10.2. Protocol amendment 3

Overall Rationale for the Amendment:

This protocol is amended primarily as a consequence of feedback from regulatory authorities of participating countries following their review of Protocol Amendment 2. Additional changes have been made to improve the clarity of the text. Table numbering and related in-text cross references have been updated from Table 18 onwards due to the inclusion of a new table in Section 8.9.

Section # and Name	Description of Change	Brief Rationale
Co-ordinating author(s)	Name of science writer updated	Change in study team members
Contributing authors	Names of US Medial Affairs Lead, and GP representatives updated.	Change in study team members.

Section # and Name	Description of Change	Brief Rationale
Cover page, page 2	Short Title changed to Title	To update to use the correct label.
Synopsis Table 1 and Table 6 Study objectives and endpoints	Footnote added to clarify that primary NI objective (MenABCWY versus MenACWY vaccines) will be assessed only in subjects without a previous MenACWY vaccination (unprimed). Correction of a typographical error.	CBER recommended to enrol a subset of subjects with a previous MenACWY vaccination (primed) to ensure adequate representation of US adolescents and young adults vaccinated in accordance with ACIP recommendations
Synopsis Table 1, Table 6, Table 12, Table 13, Section 10.1, Section 10.1.2.12, Section 10.3.4.4, Section 12.2.2	Footnote and text updated clarifying change to NHBA strain during the study will be documented in the clinical study report.	Text adjusted to clarify reporting of changes to NHBA strain will be documented in the clinical study report
Synopsis Figure 1, Synopsis (duration of the study; safety follow-up), Table 3 Schedule of Activities, Table 5 Intervals between study visits and phone calls, Section 5.2 Overall design, Figure 1, Section 5.4 Subject and study completion, Section 7.5.1 Recording of concomitant medications/products, Section 8.5.3 Safety Follow-up calls, Table 14 Reporting period for collecting safety information, Section 8.8 Study Termination Visit, Section 12.1.2 Glossary of terms; Section 12.5.9.2 Time period for detecting and recording AEs, SAEs and pregnancies; Section 12.5.12.2 Post-vaccination Visit(s)	All references to study conclusion (last subject last visit) changed to occur at Day 361, Telephone call T7.	Extended safety follow-up will be for 6 months after last study vaccination at Visit 5. This is supported by the extensive evaluation of *Bexsero* and *Menveo* safety data in clinical trials and in post marketing reports which are closely monitored through the routine pharmacovigilance activities.
Synopsis and Section 5.2 Overall design	Description of study group MenB_0_2_6 expanded. Explanatory notes referred to in the text in the bullet list were revised to clarify.	Text added to clarify that both 0,2- and 0,2,6-month schedules will be assessed in the same group. Presentation of notes associated with the text was adjusted to clarify.
Synopsis Figure 1 and Figure 1	Footnote regarding home visits amended to include reference to Section 8.9 study procedures during special circumstances	To signpost to the section providing information on study procedures during special circumstances
Table 3 Schedule of Activities / Footnote 9	Footnote 9 updated to include reference to Section 8.9 for information related to study procedures during special circumstances	To signpost to the section providing information on study procedures during special circumstances
Table 3 Schedule of Activities / Footnote 10	Footnote 10 added regarding recording of COVID-19 infection related AEs and SAEs.	To clarify diagnosis of COVID-19 should be in accordance with the WHO case definition and routine procedures for recording, evaluation, follow-up and reporting of AEs and SAEs should be in accordance with protocol-defined time periods. In addition, separate COVID-19

Section # and Name	Description of Change	Brief Rationale
		specific eCRF form(s) should be completed
Table 4 Interval between study visits	Correction of typographical error	To correct a typographical error
Section 3.1 Study rationale	Minor edit to text	Minor edit to align abbreviation use
Section 3.2 Background	Minor edit to text	Minor edit to align abbreviation use
Section 5.1 Scientific rationale for study design	Minor edits to text and wording added to rationale for 3-dose schedule	Minor edits made to text to ensure consistency in the document. Wording added to strengthen the explanation for the selection of the 3-dose schedule.
Section 6.1 Inclusion Criteria	Correction of typographical error	To correct a typographical error
Section 6.1 Inclusion Criteria	Inclusion criteria added for allowing enrolment of subjects both unvaccinated and vaccinated with MenACWY.	The study will enrol subjects both previously vaccinated and unvaccinated with MenACWY, as requested by CBER.
Section 6.2.2 Prior/Concomitant therapy	Exclusion criterion related to vaccination with previous group B meningococcal vaccines updated.	The study will allow participation of subjects primed and unprimed with MenACWY, as requested by CBER.
Section 6.3 Criteria for temporary delay for enrolment, vaccination and/or blood sampling	Criteria for temporary delay for enrolment, vaccination and/or blood sampling due to COVID-19 were added	Criteria added to clarify temporary delay for enrolment, vaccination and/or blood sampling procedures due to COVID-19
Section 6.3 Criteria for temporary delay for enrolment, vaccination and/or blood sampling	Post-vaccination window added for receiving any other non-study vaccines. Footnote updated to include seasonal influenza vaccination	To allow use of other non-study vaccines outside a specified window post-study vaccination.
Section 7.1 Treatments administered	Minor edits made to bulleted list of study vaccines/ products specific to this study	Minor edits made for clarification and consistency
Table 9 Treatments administered	Formulations for *Bexsero*, MenABCWY, *Menveo and footnote* *** were updated	Change to align the formulations for *Bexsero*, MenABCWY, *Menveo* with the certificate of analysis
Table 9 Treatments administered	Entry for placebo volume was updated and a footnote was added.	Change in placebo volume from 0.5 mL to 0.65 mL to be aligned with the certificate of analysis. A footnote was added to clarify that the volume of the pre-filled syringe administered will be within a range and the full volume should be injected.
Section 7.2.2.2.1 Study group and treatment number allocation	The minimisation procedure for the randomisation algorithm will account for previous MenACWY vaccination status (subjects with and without a previous MenACWY vaccination [primed and unprimed]).	The study will enrol subjects with and without a previous MenACWY vaccination (primed and unprimed), as requested by CBER.
Section 7.2.2.2.1 Study group and treatment number allocation	Text on site staff accessing SBIR after signing consent updated.	Any blinded site staff can access SBIR.

Section # and Name	Description of Change	Brief Rationale
Section 7.2.2.2.1 Study group and treatment number allocation	Text on freezing enrolment in a given group updated and reference added to Study Procedures Manual (SPM).	Further details will be provided in the SPM.
Section 7.2.3.1 Randomisation to strains for enc-hSBA testing	Text added to confirm the randomisation to strains for enc-HSBA testing	To enable the estimation of the correlation between each pair of strains
Section 7.3 Blinding and unblinding	Removed list of tasks of unblinded site staff.	The SPM has sufficient details.
Section 7.3 Blinding and unblinding	Sentence deleted on contacting the Sponsor in case of medical emergency.	In case of medical emergency, the investigator is allowed to unblind the study treatment immediately.
Section 7.3.1 Emergency unblinding – Table 10 Contact information for emergency unblinding	Toll-free numbers removed and reference added to SPM for individual country numbers.	Helpdesk numbers have been updated.
Section 7.5.1 Recording of concomitant medications/products and vaccinations	Sentence deleted regarding recording of all prior medications within 4 weeks of first study vaccination.	Only specific prior medications listed in this section are to be recorded in the eCRF.
Section 8.1 General study aspects	Sentence added referring to adaptation of study procedures during special circumstances.	Clarifying that procedures might be adapted during special circumstances.
Section 8.2 Data Collected from Subjects, Section 12.5.9.2 Time period for detecting and recording AEs, SAEs and pregnancies	Text added that solicited AEs ongoing after the 30-day post-vaccination period will be recorded in the eCRF.	Solicited AEs ongoing after 30 days post-vaccination period will be considered as unsolicited AEs and recorded accordingly. Clarification added that reporting of solicited AEs that have not resolved within 30 days post vaccination will be recorded in the eCRF.
Section 8.3.5 Pregnancy test	Correction of typographical error	To correct a typographical error
Section 8.4 Effectiveness and/or immunogenicity assessments	Changed future research to further research	To align with wording in the informed consent form (ICF) and electronic case report form (eCRF)
Section 8.4.3 Laboratory assays	Correction of typographical error	To correct a typographical error
Section 8.4.4.1 Immunological readouts / Table 13 Immunological read outs	Updated footnote numbering to align with the numbering in the table	To align footnote numbering with the numbering in the table
Table 14 Reporting periods for collecting safety information	Footnote added regarding COVID-19 related AEs. Abbreviation COVID-19 added to the list of abbreviations	COVID-19 infection related AEs to be reported similar to all AEs.
Section 8.5.6.2 Regulatory reporting requirements for SAEs	Correction of typographical error	To correct a typographical error
Section 8.9 Study procedures during special circumstances	Section “8.9. Study procedures during special circumstances” added.	Certain study procedures can be adapted during special circumstances such as COVID-19 pandemic.
Section 10.1.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY	Text added	To confirm demonstration of non-inferiority of MenABCWY vs MenACWY will be in subjects without a previous MenACWY vaccination (unprimed)

Section # and Name	Description of Change	Brief Rationale
Section 10.1.2.8 Immunological non-inferiority: MenABCWY vs. MenACWY in subjects without a previous MenACWY vaccination (unprimed); Table 21	Text added	To update sample size justification for the analysis of non-inferiority of MenABCWY compared to MenACWY in subjects without a previous MenACWY vaccination (unprimed) considering the study will enrol subjects with and without a previous MenACWY vaccination (primed and unprimed), as requested by CBER
Section 10.2 Population for analyses	Reference added to Statistical Analysis Plan (SAP) for list of protocol deviation leading to exclusion from analyses.	Included, as requested by CBER.
Section 10.2 Population for analyses	Sentence added to include a) sub-group analysis for secondary objectives based on previous MenACWY vaccination history (primed and unprimed); b) potential sub-group analyses assessing impact of COVID-19 pandemic.	a) Included, as requested by CBER. b) In alignment with internal and external guidance on trials conducted during the COVID-19 pandemic.
Section 10.3.3.8 Immunological non-inferiority: MenABCWY vs. MenACWY	Text added	The study will enrol subjects with and without a previous MenACWY vaccination (primed and unprimed), as requested by CBER.
Section 11 References	Three references were deleted. Two references were added to World Health Organisation documents related to the COVID-19 case definition and laboratory testing	To remove three references that linked to text deleted during Protocol Amendment 1 and Protocol Amendment 2. These references are no longer cited in the protocol. To provide references to source documents related to the COVID-19 case definition and laboratory testing
Section 12.1.1	Abbreviations COVID-19 CT, SARI and SARS-CoV-2 were added to the list of abbreviations	New abbreviations were used in the main document
Section 12.4.5.1 Responsibilities of the Investigator and IRB/EC	Correction of typographical errors	To correct typographical errors
Section 12.5.9 Detecting and recording adverse events, serious adverse events and pregnancies	Edits to existing text	To clarify procedure for distribution, use and return of Subject eDiaries
Section 12.5.9.2. Time period for detecting and recording adverse events, serious adverse events and pregnancies	Text added related to the reporting of solicited AEs not resolved within 30 days of vaccination	Solicited AEs ongoing after 30 days post-vaccination period will be considered as unsolicited AEs and recorded accordingly. Clarification added that reporting of solicited AEs that have not resolved within 30 days post vaccination will be recorded in the eCRF.
Section 12.5.9.3.2 Assessment of adverse events / Assessment of intensity	Correction of typographical error	To correct a typographical error

Section # and Name	Description of Change	Brief Rationale
Section 12.5.9.3.2 Assessment of adverse events / Assessment of causality	Edit made to existing text	Text edited to confirm all solicited local and systemic AEs
Section 12.5.9.4 Recording of AEs related to COVID-19 and Section 12.5.9.4.1 WHO Case Definition	Section added "Recording of AEs related to COVID-19"	To include the WHO COVID-19 case definition relevant to the recording of AEs related to COVID-19
Section 12.5.10.3 Back-up system in case the electronic reporting system does not work; Section 12.5.11 Updating of SAE, pregnancy, and AESI information after removal of write access to the subject's eCRF	Inclusion of email as an option for reporting AEs	To include email alongside fax as an alternative study contact following queries from site monitors as to whether this was a valid form of contact
Section 12.6.2 Contraception guidance / Table 29 Highly effective contraceptive methods	Addition of oral progestogen-only hormonal contraception	To clarify the use of oral progestogen-only hormonal contraception is acceptable

Detailed description of Protocol Amendment:

The changed text of the amendment is indicated in bold italics in the body of the protocol. The deleted text (strikethrough) and the changed text (bold italics) are provided here below.

Detailed description of Protocol Amendment 3 changes:

Cover page: Co-ordinating author(s)

PPD, Scientific Writer ***and*** PPD***, Scientific Writer for GSK***

Cover page: Contributing authors

- PPD ***and*** PPD, US Medical Affairs Lead***s***
- PPD ***and*** PPD, Global Patents

Cover page: Page 2

~~Short t~~***T****itle*

Synopsis: Objectives and Endpoints

~~All objectives and endpoints have been edited/ rewritten in Amendment 2. For readability, the entire table is not written in black bold italics. Refer to Section 0 for details.~~

Synopsis Table 1 Study objectives and endpoints

Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine*** To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the **two**~~2~~-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N. meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented ~~either in a protocol amendment or~~ in the clinical report.

Refer to Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

a post-vaccination hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and

a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

a post-vaccination‡ hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and

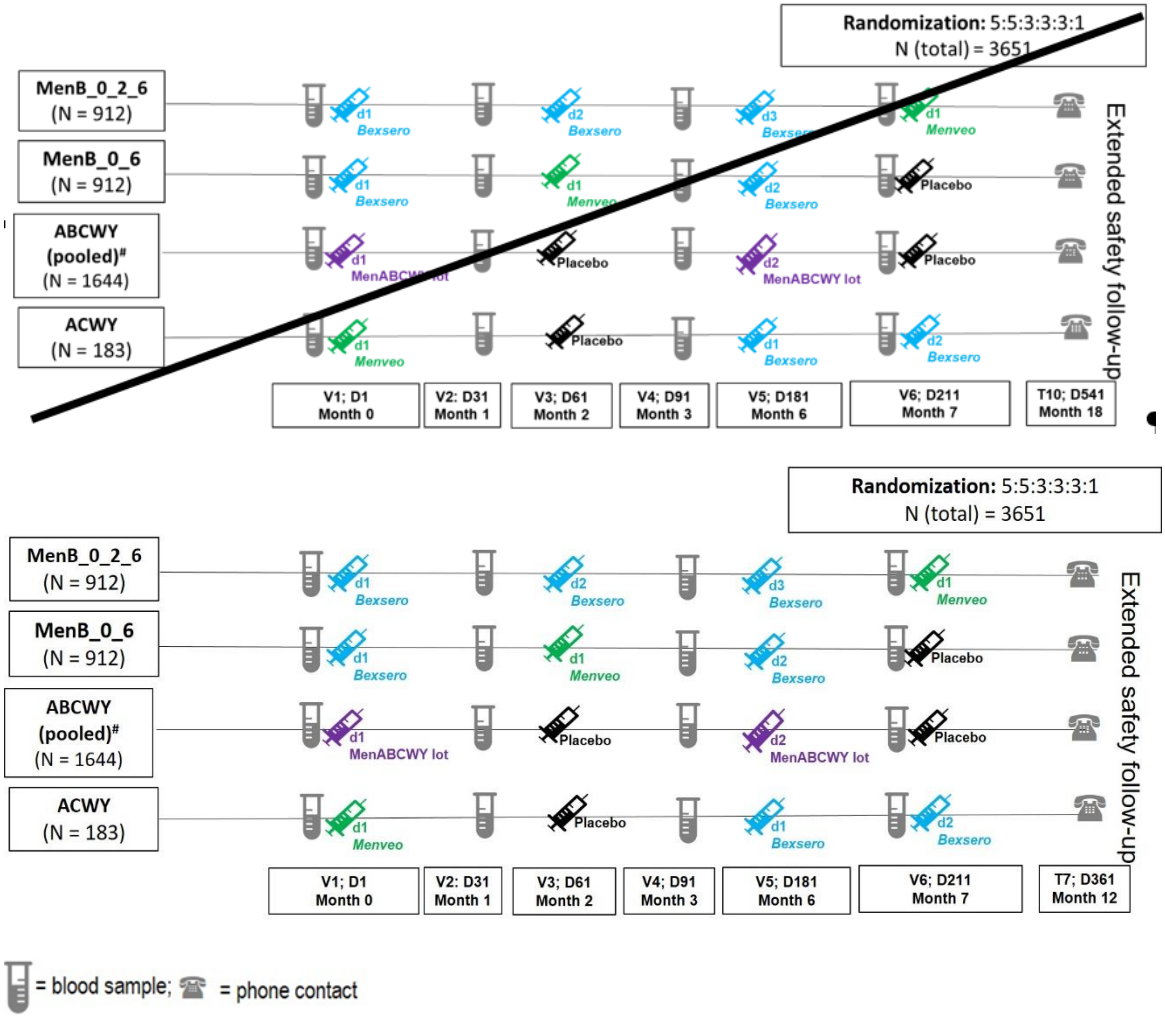
a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥ LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

******The primary objective of immunological NI of the MenABCWY vaccine to MenACWY will be evaluated only in subjects without a previous MenACWY vaccination (unprimed). All other primary and secondary objectives will be evaluated in subjects with and without previous MenACWY vaccination (primed/unprimed).***

Synopsis: Overall Design

Synopsis Figure 1 Study design overview



N = number of subjects; d = dose; V = visit; D = day; T = telephone call;
Refer to Table 3 for details on all visits
subjects will receive 2 doses of MenABCWY vaccine with Lot 1 or Lot 2 or Lot 3 of the MenACWY lyophilised vial component of the vaccine. Refer to the study groups description below the figure for details and Figure 1 for the detailed study design overview
Note**s**:
Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured.
Refer to Section 8.9 for information on study procedures during special circumstances.

A total of 3651 healthy adolescents and young adults aged 10-25 years will be enrolled and randomised (5:5:3:3:3:1 ratio) to one of the six parallel study groups:

- **MenB_0_2_6 group*:** subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (~~0,2 and~~ 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY at Day 211**. ***Data from this group will be used to assess***

both the 0,2-months and 0,2,6-months schedules; the 0,2-months schedule will be assessed 1 month after the second rMenB+OMV NZ vaccination administered at Day 61 (Visit 3), and the 0,2,6-months schedule will be assessed 1 month after the third rMenB+OMV NZ vaccination at Day 181 (Visit 5), in the same group.

- **MenB_0_6 group*:*** subjects will receive 2 doses of rMenB+OMV NZ at Day 1and Day 181 and 1 dose of MenACWY vaccine at Day 61 (0,6-months schedule). These subjects will receive 1 dose of the placebo at Day 211*~~*~~.
- **ABCWY-1****: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*~~*~~.
- **ABCWY-2****:** subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*~~*~~.
- **ABCWY-3****:** subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*~~*~~.
- **ACWY group:** subjects will receive 1 dose of MenACWY at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211*~~*~~.

*~~MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2 months vaccination schedule.~~ In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ products administered at Day 211 are not associated with any study objectives/ endpoints (***s*~~S~~afety assessment conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

** ~~**Note 1:**~~ ***(1)*** A single MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine***; (2)*** ~~**Note 2:**~~ The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot-to-lot consistency).

~~**Note 3:**~~

- Duration of the study: The study duration is approximately ~~18~~ ***12*** months for each subject.
- Safety follow-up: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call ***6*** ~~12~~ months

post-vaccination 3 (Day 181; Visit 5). This ESFU phone call ***(Day 361; T7*** ~~Day 541; T10~~***)*** will also mark the study conclusion. Refer to Table 3 and Section 8.5.3 for details on the safety follow-up.

2 Schedule of Activities

Table 3 Schedule of Activities

Age	*10 through 25 years of age at study start*															
Type of contact	**Visit**	**PC**	***Visit***	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**PC**	***PC***	~~**PC**~~	~~**PC**~~	~~**PC**~~
Visit/Phone call no.	**V1[9]**	**T1**	***V2[9]***	**V3[9]**	**T2**	**V4[9]**	**T3**	**V5[9]**	**T4**	**V6[9]**	**T5**	**T6**	***T7***	~~**T8**~~	~~**T9**~~	~~**T10**~~
Timepoint (s) [refer to Table 4 and Table 5 for visit windows]	**Day 1**	**Day 15**	***Day 31***	**Day 61**	**Day 75**	**Day 91**	**Day 121**	**Day 181**	**Day 195**	**Day 211**	**Day 241**	**Day 301**	***Day 361 (ESFU)***	~~**Day 421**~~	~~**Day 481**~~	~~**Day 541 (ESFU)**~~
Informed consent[2]	●[1]															
Informed assent, if applicable[2]	○[1]															
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●	●	●	●	●	~~●~~	~~●~~	~~●~~
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●	●	~~●~~	~~●~~	~~●~~
Recording of any AEs leading to vaccine/study withdrawal, medically attended AEs, SAEs, pregnancies and AESIs[10]	●	●	●	●	●	●	●	●	●	●	●	●	●	~~●~~	~~●~~	~~●~~
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●[7]	●	●	●	●	●	●	●	●	●	●	●	●	~~●~~	~~●~~	~~●~~
Study Conclusion[8]													●			~~●~~

[9] Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured. ***Refer to Section 8.9* for information related to study procedures during special circumstances.**

[10] Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 12.5 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 14). In addition, separate COVID-19 specific eCRF form(s) should be completed.

Table 4 Intervals between visits - footnote

[1] Subjects will not be eligible for inclusion in the ***P*er-*P*rotocol *S*et (PPS) for analysis of immunogenicity if the study visit is performed outside this interval.

Table 5 Intervals between study visits and phone calls

Interval	Length of interval	Allowed interval (Visit window)
Visit 1→T1	15 days	12 to 18 days after vaccination at V1 (from -3 to +3 days)
Visit 3→T2	15 days	12 to 18 days after vaccination at V3 (from -3 to +3 days)
Visit 3→T3	60 days	57 to 63 days after vaccination at V3 (from -3 to +3 days)
Visit 5→T4	15 days	12 to 18 days after vaccination at V5 (from -3 to +3 days)
Visit 5→T5	60 days	53 to 74 days after vaccination at V5 (from -7 to +14 days)
Visit 5→T6	120 days	113 to 134 days after vaccination at V5 (from -7 to +14 days)
Visit 5→T7 ***(ESFU; study end)***	180 days	173 to 194 days after vaccination at V5 (from -7 to +14 days)
~~Visit 5→T8~~	~~240 days~~	~~233 to 254 days after vaccination at V5 (from -7 to +14 days)~~
~~Visit 5→T9~~	~~300 days~~	~~293 to 314 days after vaccination at V5 (from -7 to +14 days)~~
~~Visit 5→T10 (ESFU; study end)~~	~~360 days~~	~~353 to 381 days after vaccination at V5 (from -7 to +21 days)~~

Section 3.1 Study rationale

In 2013, the ***United States (***US***)*** Food and Drug Administration (FDA) agreed with the Company proposal to evaluate meningococcal B vaccine effectiveness against a large panel of the US epidemiologically relevant invasive disease strains of *Neisseria meningitidis* ***(N. meningitidis)*** serogroup B in adolescents using serum bactericidal assay with endogenous human complement (enc-hSBA). This panel includes 110 serogroup B strains selected from the original panel of 442 endemic strains identified as appropriately representative of invasive meningococcal serogroup B strains detected in the US by the US Centers for Disease Control (CDC) [Welsch, 2018]. Following licensure of *Bexsero* (rMenB+OMV NZ) in the US in 2015, under accelerated approval regulations, GSK was requested to demonstrate effectiveness of *Bexsero* via a post-approval confirmatory trial in US adolescents and young adults.

Study 3.2 Background

N.~~eisseria~~ *meningitidis* is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. *N. meningitidis* infections causing invasive meningococcal disease (IMD) are an important public health concern worldwide due to the substantial morbidity and mortality they cause, as well as the transmissibility of these infections. In healthy individuals, IMD can rapidly progress to serious clinical disease and may be associated with poor outcomes, including fatality in

~10% of cases. While the greatest IMD burden is in infants, there is a second peak of disease in adolescents and young adults.

…. In the EU, the vaccine is indicated for use in individuals 2 years of age and older, and in the ~~United States (~~US~~)~~, in individuals 2 months to 55 years of age.

Bexsero is indicated for active immunisation against invasive disease caused by ~~*Neisseria meningitidis (*~~***N. meningitidis***~~)~~ serogroup B.

Section 4 Objective(s) and Endpoint(s)

Table 6 Study objectives and endpoints

Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine*** To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the last MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination. *Criterion:* *LL of the* ***two***~~2~~*-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	The percentages of subjects with 4-fold rise* in hSBA titres against *N. meningitidis* serogroups A, C, W and Y at 1 month after the: • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • 1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N. meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented ~~either in a protocol amendment or~~ in the clinical report.

Refer to Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of Terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

*For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:

a post-vaccination hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and

a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

**For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:

a post-vaccination‡ hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4

a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and

a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥ LLOQ

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule).

******The primary objective of immunological NI of the MenABCWY vaccine to MenACWY will be evaluated only in subjects without a previous MenACWY vaccination (unprimed). All other primary and secondary objectives will be evaluated in subjects with and without previous MenACWY vaccination (primed/unprimed).***

Section 5.1 Scientific rationale for study design

As the rMenB+OMV NZ licensure in the US was issued through accelerated approval, the FDA has requested to demonstrate the effectiveness of the vaccine against an extended panel of serogroup B meningococcal strains (MenB) as a post-marketing commitment in US adolescents and young adults, thus confirming that the vaccine can protect against diverse meningococcal B strains prevalent in the ~~United States~~***US.***

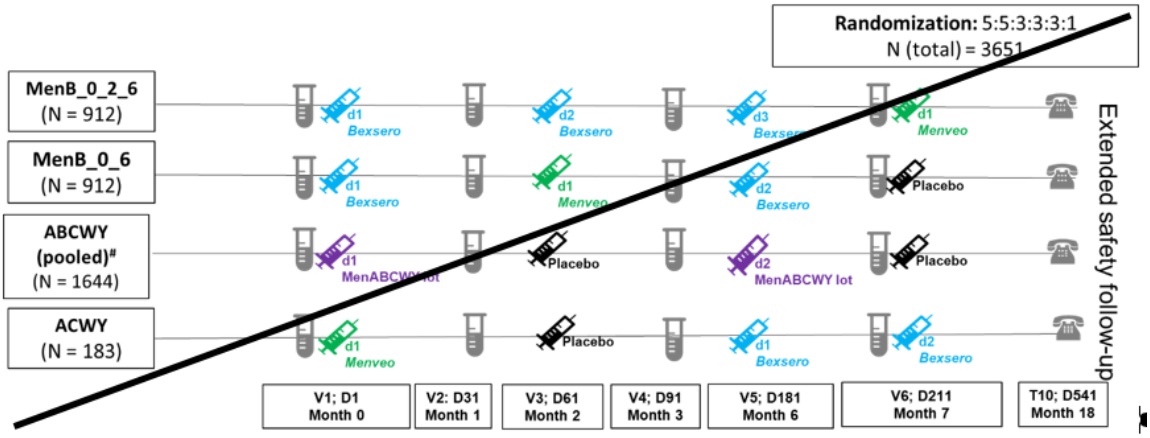
The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections and could increase coverage for meningococcal disease caused by *N. meningitidis* serogroups A, B, C, W, and Y worldwide. GSK's investigational MenABCWY combination vaccine is intended to protect against 5 of the most prevalent serogroups of ~~*Neisseria*~~ ***N.*** *meningitidis* (A, B, C, W, Y) in humans.

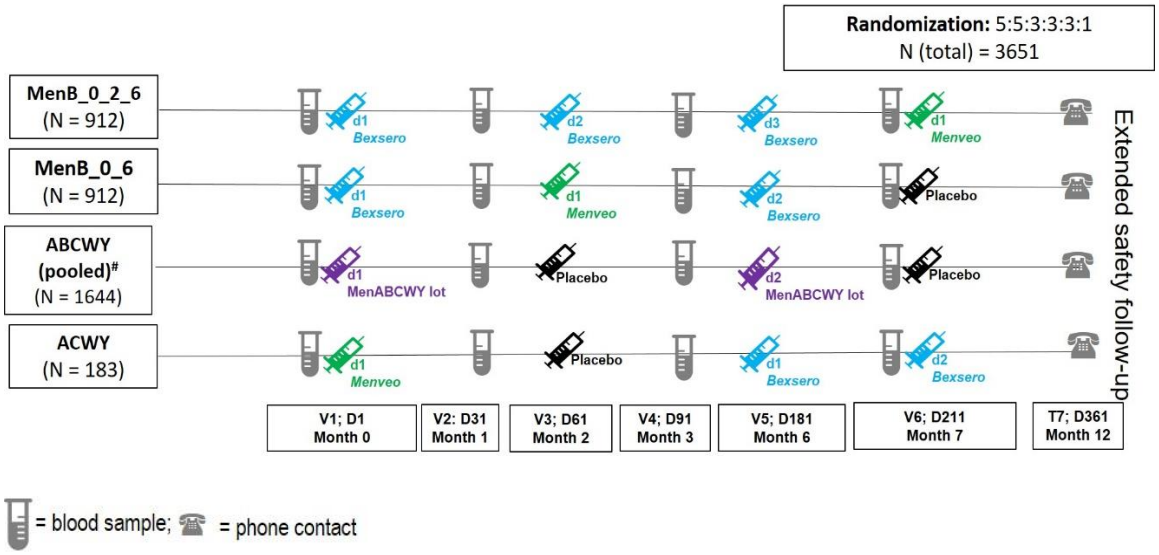
Rationale for the selected vaccination schedules

rMenB+OMV NZ: This study aims ~~at~~ ***to demonstrate*** ~~demonstrating~~ the VE of the rMenB+OMV NZ vaccine administered as 2-dose vaccine, either with a shorter interval (0,2-months) or a prolonged interval (0,6-months) between doses. A 3-dose schedule has ***also*** been ~~also~~ added to better characterise the VE ***with an alternative dose regimen as a post approval requirement from the US FDA***.

Section 5.2 Overall design

Figure 1 Study design overview





= blood sample; ☎ = phone contact

N = number of subjects; d = dose; V = visit; D = day; T = telephone call;
Refer to Table 3 for details on all visits
subjects will receive 2 doses of MenABCWY vaccine with Lot 1 or Lot 2 or Lot 3 of the MenACWY lyophilised vial component of the vaccine. Refer to the study groups description below the figure for details and Figure 1 for the detailed study design overview
Note**s**:
Home visits may be performed only by sites authorised (as per local regulations and sponsor agreement), with approved site level standard operating procedures (SOP) provided that the compliance with protocol procedures are ensured
Refer to Section 8.9 for information on study procedures during special circumstances.

Section 5.2 Overall design

- **MenB_0_2_6 group*:** subjects will receive 3 doses of rMenB+OMV NZ at Day 1, Day 61 and Day 181 (~~0,2 and~~ 0,2,6-months schedule). These subjects will receive 1 dose of the MenACWY at Day 211**. ***Data from this group will be used to assess both the 0,2-months and 0,2,6-months schedules; the 0,2-months schedule will be assessed 1 month after the second rMenB+OMV NZ vaccination administered at Day 61 (Visit 3), and the 0,2,6-months schedule will be assessed 1 month after the third rMenB+OMV NZ vaccination at Day 181 (Visit 5), in the same group.***
- **MenB_0_6 group*:** subjects will receive 2 doses of rMenB+OMV NZ at Day 1and Day 181 and 1 dose of MenACWY vaccine at Day 61 (0,6-months schedule). These subjects will receive 1 dose of the placebo at Day 211**.
- **ABCWY-1****: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.
- **ABCWY-2****: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilised vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211**.
- **ABCWY-3****: subjects will receive 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilised

vial component of the vaccine. They will receive 1 dose of placebo at Day 61 and at Day 211*~~*~~.

- **ACWY group:** subjects will receive 1 dose of MenACWY at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211*~~*~~.

~~*MenB_0_2_6 group will also be evaluated for objectives pertaining to 0,2 months vaccination schedule.~~ In order to let the subjects in MenB_0_2_6 group receive a dose of MenACWY vaccine and for subjects in ACWY group to receive the second dose of rMenB+OMV NZ in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the US [ACIP, 2011]), the subjects in these groups will receive a vaccination of MenACWY and rMenB+OMV NZ vaccines, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, subjects in the rest of the groups (MenB_0_6, ABCWY-1, ABCWY-2 and ABCWY-3) will receive a dose of Placebo. All these vaccines/ products administered at Day 211 are not associated with any study objectives/ endpoints (***s*~~S~~afety assessment conducted after 1 dose of rMenB+OMV NZ in the ACWY group at Day 181 is to maintain the blind of the study).

*** ~~**Note 1:**~~ ***(1)*** A single MenB lot will be used for the pre-filled syringe component of the MenABCWY vaccine***; (2)*** ~~**Note 2:**~~ The groups ABCWY-1, ABCWY-2, ABCWY-3 will be pooled into a single group, ABCWY (pooled lots) (except for analysis of lot-to-lot consistency).

~~**Note 3:**~~

- Duration of the study: The study duration is approximately ~~18~~ ***12*** months for each subject.
- Primary completion Date (PCD): (~~T10; Day 541~~ ***Day 361; T7***).

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): the date of release of the last testing results, to be achieved not later than 8 months after Last Subject Last Visit (LSLV) (LSLV = ***T7***)~~Day 541; T10~~. If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.

Refer to glossary of terms for the definition of EOS.

- Safety monitoring: Regular safety follow-up will be done through telephone calls (T). There will also be an extended safety follow-up (ESFU) phone call ~~12~~ ***6*** months post-vaccination 3 (Day 181; Visit 5). This ESFU phone call (***Day 361; T7***) will also mark the study conclusion. Refer to Table 3 and Section 8.5.3 for details on the safety follow-up.

Section 5.4. Subject and study completion

A subject is considered to have completed the study, if the subject is available for the concluding contact (***Day 361; T7*** ~~T10; Day 541~~) as described in the protocol.

Section 6.1 Inclusion criteria for enrolment

- Subjects or/and subjects' parent(s)/Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the eDiar~~y~~***ie***s, return for follow-up visits and is available for telephone calls).
- ***Subjects who are either unvaccinated with MenACWY vaccine or have received a single previous dose of MenACWY vaccine can participate in the study, if they have received it at least 4 years prior to informed consent and assent as applicable (with the exception of meningococcal C vaccination, if the last dose of MenC was received at ≤24 months of age).***

Section 6.2.2 Prior/Concomitant therapy

- ***Previous vaccination against any group B meningococcal vaccine at any time prior to informed consent and assent as applicable.*** ~~Previous vaccination with any meningococcal (MenB or MenACWY) vaccine at any time prior to informed consent/ assent (as applicable) with the exception of meningococcal C (conjugated or polysaccharide) vaccination, if the last dose of MenC was received at ≤24 months of age.~~

Section 6.3 Criteria for temporary delay for enrolment and vaccination and/or blood sampling

- ***A positive test for current infection with COVID-19. The testing should have been done using a molecular (polymerase chain reaction [PCR] or antigen test) approved by the country regulatory authorities.***
- ***Subjects with known COVID-19 positive contacts in the past 14 days.***
- Individuals who have received any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to ***and following*** each vaccination up to Visit 5*.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

  In case of seasonal influenza vaccination, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations.

Section 7.1 Treatments administered

The study vaccines/ products specific to this study are described below.

- rMenB+OMV NZ (GSK's Meningococcal Group B Vaccine, *Bexsero*)***;***
- MenABCWY (GSK's combined investigational Meningococcal Groups A, B, C, W and Y Vaccine)***;***
- MenACWY (GSK's Meningococcal Groups A, C, W, and Y conjugate Vaccine, *Menveo*)***;***
- Placebo***.***

Table 9 Treatments administered

Study Treatment Name:	*Bexsero*	MenABCWY#		*Menveo****		Placebo
Vaccine(s)/Product(s) name	rMenB+OMV NZ	MenACWY lyo	rMenB+OMV NZ	MenA	MenCWY	NaCl
Presentation	Syringe	Vial	Syringe	Vial	Vial	Syringe
Dose form	Suspension for injection	Powder for suspension for injection	Suspension for injection	Powder for solution for injection	Solution for injection	Solution for injection
Vaccines/ product formulation†:	~~Recombinant *N. meningitidis* serogroup B~~ NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; ~~Recombinant *N. meningitidis* serogroup B~~ NadA protein (50 µg) adsorbed on aluminium hydroxide; ~~Recombinant *N. meningitidis* serogroup B~~ fHBP fusion protein (50 µg) adsorbed on aluminium hydroxide; ~~Outer membrane vesicles~~ ***OMV*** from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); ~~Sucrose; Histidine; Sodium chloride;~~ Water for injections q.s. 0.5 mL	MenA(10 µg)-CRM_{197}; MenC(5 µg)-CRM_{197}; MenW135(5 µg)-CRM_{197}; MenY(5 µg)-CRM_{197}	~~Recombinant *N. meningitidis* serogroup B~~ NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; ~~Recombinant *N. meningitidis* serogroup B~~ NadA protein (50 µg) adsorbed on aluminium hydroxide; ~~Recombinant *N. meningitidis* serogroup B~~ fHBP fusion protein (50 µg) adsorbed on aluminium hydroxide; ~~Outer membrane vesicles~~ ***OMV*** from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); ~~Sucrose; Histidine; Sodium chloride;~~ Water for injections q.s. 0.5 mL	***MenA(10 µg)-CRM_{197} (16.7–33.3 µg)*** ~~Meningococcal group A oligosaccharide (10 µg) conjugated to *Corynebacterium diphtheriae* (CRM_{197}) protein (16.7-33.3 µg); Potassium dihydrogen phosphate; Sucrose~~	***MenC(5 µg)-CRM_{197} (7.1–12.5 µg); MenW135(5 µg)-CRM_{197} (3.3–8.3 µg); MenY(5 µg)-CRM_{197} (5.6–10 µg); water for injections q.s. 0.5 mL*** ~~Meningococcal group C oligosaccharide (5 µg) conjugated to Corynebacterium diphtheriae (CRM_{197}) protein (7.1-12.5 µg); Meningococcal group W-135 oligosaccharide (5 µg) conjugated to Corynebacterium diphtheriae (CRM_{197}) protein (3.3-8.3 µg); Meningococcal group Y oligosaccharide (5 µg) conjugated to Corynebacterium diphtheriae (CRM_{197}) protein (5.6-10 µg); Sodium chloride; Sodium dihydrogen phosphate~~	***Sodium chloride (NaCl) (0.9%); Water for injections***

Study Treatment Name:	*Bexsero*	MenABCWY#	*Menveo****	Placebo
			~~monohydrate; Disodium phosphate dihydrate; Water for injections q.s. 0.5 mL~~	
Route of Administration	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use
Administration site:				
Location	Deltoid	Deltoid	Deltoid	Deltoid
Laterality*	Non-dominant	Non-dominant	Non-dominant	Non-dominant
Number of doses to be administered:				
• MenB_0_2_6 group	3	-	1	-
• MenB_0_6 group	2	-	1	*1*
• ABCWY-1 group	-	2	-	*2*
• ABCWY-2 group	-	2	-	*2*
• ABCWY-3 group	-	2	-	*2*
• ACWY group	2	-	1	*1*
Volume to be administered**	0.5 mL	0.5mL	0.5 mL	***0.65*** mL****
Packaging and Labelling Do not include a sample of the label text or details of pack design in the protocol. It will be specified in the SPM	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK Biologicals SA	GSK Biologicals SA	GSK Biologicals SA	GSK Biologicals SA

OMV = Outer Membrane Vesicles; SPM = study procedure**s** manual

**** ***The volume of the saline pre-filled syringe may be between 0.6ml and 0.8 mL. The full volume is to be injected.***

Section 7.2.2.2.1 Study group and treatment number allocation

The target will be to enrol a total of 3651 eligible subjects who will be randomly assigned to 6 study groups in a 5:5:3:3:3:1 ratio (912 each in MenB_0_2_6 and MenB_0_6 groups, 548 in each ABCWY group and 183 in ACWY group).

Allocation of the subject to a study group/a treatment number at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for study, region (US and ex-US countries)***, previous MenACWY vaccination? (Yes and No)****,* and age category (10-17 years of age and 18-25 years of age). Minimisation factors will have equal weight in the minimisation algorithm.

To ensure adequate representation in the US in line with the post-marketing commitment (Section 3.1), a minimum of 30% of adolescents and young adults will be enrolled in the US.

After obtaining the signed and dated ICF/IAF from the subject/subject's parent/LAR and having checked the eligibility of the subject, ~~the~~ ***blinded*** site staff ~~in charge of the vaccine/product administration~~ will access SBIR. Upon providing the subject identification number, ***the subject's age category and previous MenACWY vaccination? (Yes/ No)****,* the randomisation system will determine the study group and will provide the treatment number to be used for each dose. ~~Region does not have to be given as an input by the site staff as SBIR deduces it from the site ID.~~

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 SPM for specific instructions.

If for any reason, after randomisation the subject fails to undergo treatment, this is an early Termination and the reason should be recorded in source document as specified in the SDA.

Note that ***enrolment will be frozen*** as soon as the target number***s (Table 7) are reached*** ~~in a group has been reached~~. ***Refer to the SPM for further details.*** ~~(refer to Table 7), the enrolment will be frozen for this group.~~

Note: * Subjects with and without a previous MenACWY vaccination (primed and unprimed).

Section 7.2.3.1 Randomisation to strains for enc-hSBA testing

The evaluation of the randomly selected panel of invasive serogroup B strains (110 strains) for each vaccinated subject is not technically feasible with clinically acceptable blood volumes drawn from adolescents and young adults. ~~Thus, in addition to randomisation of enrolled subjects to the rMenB+OMV NZ or MenABCWY and ACWY groups,~~ ***For each applicable serum sample, 35 strains will be chosen completely at***

random from the 110 strains. ~~subjects will be randomly assigned to a starting strain resulting in a list of planned strains [from the 110-panel] per subject per acquired blood sample of sufficient volume for testing.~~

- ~~These strains were randomly ordered into a testing sequence. This testing sequence will be used to define a list of strains to be tested for each subject. Within each study group, each subject will be randomly assigned to a start strain in the pre-ordered sequence of 110 invasive disease serogroup B strains (e.g., strain 1 or 5 or 101). The randomisation algorithm will use a block size of 110 (i.e., a start strain will not be repeated for 110 subjects within each block), to ensure as much as possible, a similar number of subjects tested for each strain.~~
- The target number of strains to be tested for each subject will be 35 strains.
- The serum sample collected from each subject will be sent on an ongoing basis to GSK Clinical Laboratory Sciences or to laboratories delegated by GSK where the assays are available and qualified for the intended use. Aliquots for immunogenicity and enc-hSBA testing will be prepared depending on the serum volume available for a visit from one subject. A minimum amount of 5 mL of serum needs to be available to confirm eligibility to perform enc-hSBA testing. Additional instruction on the number of strains to be randomly assigned for enc-hSBA testing, according to the actual sample volume of serum provided to the laboratory, is provided in Section 10.1.2.

Section 7.3 Blinding and unblinding

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine(s)/product(s) recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity, and effectiveness) will all be unaware of which vaccine/product was administered. To do so, vaccine/product preparation and administration will be done by qualified healthcare professional who will not participate in any of the study clinical evaluation. A minimum number of study site personnel responsible for preparing and / or delivering the injections will be unblinded. See Glossary of terms for definition of qualified healthcare professional and unblinded study staff. ~~The tasks of the unblinded site staff are limited to storage, registration of the storage temperature, drug accountability, preparation and administration of the study vaccines. No other tasks are to be performed.~~ Site personnel responsible for delivering the injection must not be involved in study assessments. The study vaccine / placebo will be provided to the site as subjects' kits, similar in appearance, identified with treatment information (either Meningococcal Group B Vaccine or Meningococcal Groups A, B, C, W and Y Vaccine or Meningococcal Groups A, C, Y and W Conjugate Vaccine or placebo). Refer to SPM for details.

~~Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance of medical emergency, every effort should be made to contact the Sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator (See Section 7.3.1).~~

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

The serological data, which could lead to the unblinding of the study groups, will not be available during the course of the study to any investigator or any person involved in the clinical conduct of the study or analysis.

Section 7.3.1 Emergency unblinding / Table 10

Table 10 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email ~~***For US only Toll Free: + 1 844 446 3133***~~ ~~***Toll-free number: 877 870 0019;***~~ ~~Turkey: 800 621 95 95~~ Phone: +32 2 656 68 04 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

Refer to SPM for other country-specific numbers.

Section 7.5.1 Recording of concomitant medications/products and concomitant vaccinations

All medications and vaccines taken or received by the subject within 4 weeks prior to the first study vaccination and all the blood products, corticosteroids (PO/IV/IM), antineoplastic and immunomodulating agents or radiotherapy taken or received by the subject within 90 days prior to the start of the study are considered prior medications and are to be recorded on the Prior and Concomitant Medications eCRF. Concomitant medications include all medications taken by/administered to the subject at and after enrolment to treat any AE collected in the eCRF and any vaccine administered to subjects. These medication***s***/ vaccine***s*** must be documented on the Prior and Concomitant Medications and Vaccination eCRF.

- Any concomitant vaccination administered in the period starting 14 days before the first dose of study vaccine(s)/product(s) and ending at the last study contact (Day -14 to Day ***361***~~541~~).

Section 8.1 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.

During special circumstances, exemplified by the COVID-19 pandemic, certain study procedures may be adapted to protect the subject and promote data integrity. Refer to Section 8.9 for further details.

Section 8.2 Data collected from Subjects

- Post-vaccination solicited local and systemic AEs collected at home by subject and/or subject's parent(s)/LAR(s) and recorded in the Subject eDiary for 7 days following each vaccination visit (at Day 1, Day 61 and Day 181). Any ongoing event (beyond 7 days) may be followed up for 30 days or until resolution, whichever is earlier, in the eDiary. ***Any solicited AE that has not resolved within 30 days post vaccination and is reported during clinic visits or safety follow-up calls will be entered into the subject's eCRF as an unsolicited AE. It will also be included in the subject's source documents at the site by the investigator/site staff as a verbally reported event. It will not be included in the Subject eDiary. These AEs will be analyzed as unsolicited AEs (i.e. in the Unsolicited Safety Set).***

Section 8.3.5 Pregnancy test

Urine samples will be collected for pregnancy testing in females of child-bearing potential, before vaccinations at Visits 1, 3, 5 and 6, and the results recorded in the source document and the eCRF.

Section 8.4 Effectiveness and/or immunogenicity assessments

Future findings may make it desirable to use the samples acquired in this study for ~~future~~ ***further*** research, not described in this protocol. Additional serological testing may be performed in the future to further characterise the antibody response to the antigens included in the study vaccines or hSBA against an additional panel of strains of *Neisseria* species.

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~~ ***further*** research. ~~Future~~ ***Further*** research will be subject to prior EC/IRB approval if required per local legislation.

Section 8.4.3 Laboratory assays

An Enzyme-Linked Immunosorbent Assay (ELISA) will be used to evaluate the serotype-specific IgG responses to A, C, W, and Y. The intent is to ~~characterise~~***characterize*** whether the immunogenicity measured by hSBA using the MenA, C, W and Y indicator strains may be confounded by the contribution of the responses against the MenB antigens of the combination vaccine. The ELISA procedure is used to detect the amount of serum immunoglobulin G (IgG) antibodies in response to specific *N. meningitidis* polysaccharide antigens.

Table 12 Laboratory assays – table footnote

* Strain(s) and/or assay cut-off(s) might be subject to change during the course of the study (e.g. in case of new qualification, (re-)validation or standardisation). In this case, this will be documented ~~either in a protocol amendment or~~ in the clinical report.

Section 8.4.4.1 Immunological read-outs / Table 13 Immunological read-outs – table footnotes

~~1~~2 For detail regarding the method refer to Table 12.

~~2~~3 The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented ~~either in a protocol amendment or~~ in the clinical report.

Section 8.5.3 Safety Follow-up Calls

Safety follow-up phone calls are made on Day 15 (T1), Day 75 (T2), Day 121 (T3), Day 195 (T4), Day 241 (T5), Day 301 (T6), ***and*** Day 361 (T7)~~, Day 421 (T8), Day 481 (T9) and Day 541 (T10)~~. Safety follow-up calls are made to the subject by a qualified healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject and/or parent(s)/legal guardian(s) will be interviewed at Day 15 (SFU 1; T1), Day 75 (SFU 2; T2) and Day 195 (SFU 4; T4) according to the script, and information relating to any unsolicited AEs will be collected.

At all safety follow-up phone calls (T1 **to T**~~7~~10) information relating to SAEs, AESIs, medically attended AEs and AEs leading to withdrawal will be collected. At all Safety Follow-up Calls concomitant medications associated with the AE and concomitant vaccinations have to be collected. All safety information described by the subject must be written down in a designated location within the source document ~~and not written on the script used for the telephone call.~~ ***If this script is used as a source document, ensure that it meets the definition of a source document as per ICH GCP and/or local requirements.***

The site should schedule the next study activity clinic (visit or safety call) with the subject and/or parent(s)/LAR(s).

The subject and/or parent(s)/legal guardian(s) will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalisation or an emergency room visit.

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Section 8.5.4 Time period and frequency for collecting AE and serious adverse event (SAE) information – Table 14 Reporting period for collecting safety information, removal of last three columns of table

Event	On V1*	V1		V2	V3		V4	V5		V6			*Study Conclusion*	~~Study Conclusion~~		
		D1***	D7	D31	D61	D67	D91	D181	D 187	D 211	D241	D301	D 361	~~T10~~ ~~D421~~	~~D481~~	~~D541~~
Solicited local and systemic AEs																
Unsolicited AEs																
AEs leading to withdrawal from the study																
Medically attended AEs**																
SAEs																
SAEs related to study participation or concurrent GSK medication/vaccine																
AESIs																
Pregnancies																

.; V: Visit; D: Day, M: Month; T,Telephone call***; COVID-19, Coronavirus Disease 2019***

* i.e. consent obtained

*** Including COVID-19 infection related AEs.***

*** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration.

Section 8.5.6.2 Regulatory reporting requirements for SAEs

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAE***s***) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Section 8.8. Study Termination Visit/ Study Conclusion

The study termination call will occur on Day ***361***~~541~~. The termination visit will be a phone call (also in case of early termination of the study).

The date of termination is the date of the last contact (telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see Section 8.8.1.

During the phone call at the end of the study (Day ***361***~~541~~), the following procedures will be performed: interview of subject and/or parent(s)/legal guardian(s) to collect SAEs, AESIs, medically attended AEs, pregnancies and/or concomitant medications/ vaccinations.

Section 8.9 Study procedures during special circumstances

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 subjects:

- ***If the Subject eDiary device was provided to the subject, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 6).***
- ***Study visits may be performed-at a different location* other than the study site (e.g. at subject's home). For study visits involving blood draw, biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***
- ***If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 4), then the interval may be extended as described below in Table 17.***
- ***If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Table 4 then the interval may be extended as described below in Table 17.***

  **** It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location.***

This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site.

In case of home visits, the study procedures should be carried out by a qualified person/s as delegated by the Principal Investigator, provided that the compliance with protocol procedures are ensured. Refer to Schedule of Activities for the schedule of visits (see Table 3).

Refer to local regulations on the conduct of clinical trials during the COVID-19 (Coronavirus) pandemic for more details.

Impact on the per protocol set for immunogenicity will be determined on a case by case basis.

Table 17 Intervals between study visits during special circumstances

Interval	Length of interval	Allowed interval (Visit window)
Visit 1 → Visit 2	30 days	23 to 51 days after vaccination at V1 (from -7 to +21 days)
Visit 1→Visit 3	60 days	53 to 81 days after vaccination at V1 (from -7 to +21 days)
Visit 3→Visit 4	30 days	23 to 51 days after vaccination at V3 (from -7 to +21 days)
Visit 3→Visit 5	120 days	110 to 148 days after vaccination at V3 (from -10 to +28 days)
Visit 5→Visit 6	30 days	23 to 51 days after vaccination at V5 (from -7 to +21 days)

Section 10.1 Sample size determination

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented ~~either in a protocol amendment or~~ in the clinical report.

Section 10.1.1.8. Immunological non-inferiority: MenABCWY vs. MenACWY

For demonstration of non-inferiority of MenABCWY vs MenACWY ***in subjects without a previous MenACWY vaccination (unprimed)***, the following non-inferiority hypotheses will be tested simultaneously for each of the 4 serogroups A, C, W, and Y:

Section 10.1.2.8 Immunological non-inferiority: MenABCWY vs. MenACWY *in subjects without a previous MenACWY vaccination (unprimed)*

~~One thousand two hundred thirty three (1233) evaluable subjects in the ABCWY group (pooled lots) at 1 month after the last vaccination and 137 in the ACWY group at 1 month after the MenACWY vaccination (at Month 7 for ABCWY group (pooled lots) and at Month 1 for ACWY group)~~ ***Assuming at least 70% subjects without a previous MenACWY vaccination (unprimed), there will be at least 863 (70% out of 1233) evaluable subjects in the ABCWY group (pooled lots), at 1 month after the last vaccination, and 96 (70% out of 137) in the ACWY group at 1 month after the MenACWY vaccination (at Month 7 for ABCWY group (pooled lots) and at Month 1 for ACWY group). This sample size*** is sufficient to demonstrate that the lower limit of

the two-sided 97.5% CIs for by percentage of subjects with 4-fold rise in hSBA titres against MenACWY indicator strains A, C, W and Y is > -10%.

Assuming similar underlying immune response after 2 doses of MenABCWY vaccine, as previously observed in study V102_16 (Column 2 and 3 of Table 21), the resulting overall power is 99.6%.

Table 21 Power calculation to demonstrate non-inferiority for serogroups A, C, W and Y of MenABCWY compared to MenACWY *in subjects without a previous MenACWY vaccination (unprimed)*, at 1 month after the second dose vs 1 month after a single dose

Serogroup	*MenABCWY % 4-fold rise (2 doses)*	*MenACWY % 4-fold rise (1 dose)*	*Power (%) for 70% subjects unprimed with MenACWY*
A	92.4%	59.1%	>99.9%
C	95.4%	56.9%	>99.9%
W	80.4%	34.0%	>99.9%
Y	90.9%	62.8%	>99.9%
Total			99.6%

Unprimed subjects = Subjects without a previous MenACWY vaccination

Section 10.1.2.12 Non inferiority of MenABCWY vs rMenB+OMV NZ measured by percentage of subjects with 4-fold rise in hSBA titres against MenB component indicator strains post 2nd dose

*The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented ~~either in a protocol amendment or~~ in the clinical report.

Section 10.2 Populations for analyses

For analyses of the safety endpoints, subjects will be analysed "as treated" according to the actual vaccination a subject received. ***The list of protocol deviations that would result in exclusion from the PPS is available in Section 4.2.2.1 of the Statistical Analysis Plan.***

Subgroups:

- Analyses of the primary objectives will be repeated by age group (10-17 years of age and 18-25 years of age), race, sex and ~~the~~ US region***, , and subjects with and without a previous MenACWY vaccination (primed and unprimed) as relevant.***
- ***Additional subgroup analyses may be performed to assess the impact of any COVID-19 pandemics. More details will be provided in the Statistical Analysis Plan if applicable.***

Section 10.3.3.8 Immunological non-inferiority: MenABCWY vs. MenACWY

10.3.3.8 Immunological non-inferiority: MenABCWY vs. MenACWY *in subjects without a previous MenACWY vaccination (unprimed)*

Section 10.3.4.4 Immune response of MenABCWY, rMenB+OMV NZ and Men ACWY

* The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented ~~either in a protocol amendment or~~ in the clinical report.

Section 11 References

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~~Harrison O, Claus H, Jiang Y. Epidemiology and nomenclature of N. meningitides capsule locus. Emerging Infectious Diseases 2009 19(4):566-573.~~

~~Health Protection Agency. (2006) Laboratory reports of invasive meningococcal infections, England and Wales: weeks 46 to 52 2005; Enhanced surveillance of meningococcal disease: October to December 2005. CDR Weekly [serial online]; 16(8).~~

World Health Organization (WHO). Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance. WHO, 2019 [cited 11-SEP-2019] Available from: https://www.who.int/publications/i/item/10665-331501

World Health Organization (WHO). WHO COVID-19 Case Definition. WHO, 2020 [cited 11-SEP-2019] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1

Section 12.1.1. List of abbreviations

The following abbreviations were added to the existing list of abbreviations:

COVID-19:	***Coronavirus disease 2019***
CT:	***Computed tomography***
2019-nCoV:	***2019 novel coronavirus disease***
SARI:	***Severe Acute Respiratory Illness***

Section 12.1.2 Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (***T7*~~T10~~**). or Last testing results released of samples collected at Visit 6* * In this case EoS must be achieved no later than 8 months after LSLV.

Section 12.2.2 MenB serum bactericidal assays using exogenous human complement (hSBA) – rMenB + OMV NZ

The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented ~~either in a protocol amendment or~~ in the clinical report.

Section 12.4.5.1 Responsibilities of the Investigator and IRB/EC

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/~~favorable~~ ***favourable*** opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

i. to the IRB/IEC for review and approval/~~favorable~~***favourable*** opinion,

Section 12.5.9 Detecting and recording adverse events, serious adverse events and pregnancies

~~Subjects eDiaries will be distributed to~~ ***Each*** subjects/subject's parent(s)s/LAR(s) ***will be assigned a Subject eDiary at Visit 1 and shown how to use the device – this will include how to access the diary, performing test data entry on sample questions, and how to charge and store the device.*** ~~at each vaccination visit on Visit 1, Visit 3 and Visit 5.~~

The subject/subject's parent(s)/LAR(s) ~~will have to~~ ***must*** ~~return~~ ***bring*** their completed eDiaries ~~on~~ ***at*** Visit 2~~,~~ and Visit 4, and ***return it at*** Visit 6. The returned Subject eDiaries should be verified during discussion with the subject/ subject's parent(s)/LAR(s) at these visits.

Note: If the ~~diary card~~ ***Subject eDiary*** has been filled in by a minor subject, the investigator or delegate should verify the reported information during a discussion with the minor subject preferably in the presence of his/her parent(s)/LAR(s).

Section 12.5.9.2. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All solicited AEs during 7 days following administration of each dose of study vaccine(s)/product(s) (Day 1 to Day 7) (at Visit 1, Visit 3 and Visit 5) must be recorded in the eDiary, irrespective of intensity ~~or whether or not they are considered vaccination-related~~. Solicited local and systemic events that are ongoing after the 7-day reporting period may continue to be recorded in the eDiary until resolution or up to 30 days post-vaccination (ie, recording period for unsolicited AEs) whichever occurs first and do not need to be entered as an AE in the AE eCRF or the subject's source document. ***Any solicited AE that has not resolved within 30 days post vaccination and is reported during clinic visits or safety follow-up calls will be entered into the subject's eCRF as an unsolicited AE. It will also be included in the subject's source documents at the site by the investigator/site staff as a verbally reported event. It will not be included in the Subject eDiary. These AEs will be analysed as unsolicited AEs (i.e. in the Unsolicited Safety Set).***

All other AEs during 30 days following administration of each dose of study vaccine(s)/product(s) (Day 1 to Day 30) (at Visit 1, Visit 3 and Visit 5) must be recorded in the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine(s)/product(s) and will end ***6***~~12~~ months following administration of the study vaccines (***Day 361***~~541~~ (***T***7~~10~~) for each subject. See Section 12.5.10 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.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccines until study end.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccines and will end ***6***~~12~~ months following administration of study vaccines (***Day 361***~~541~~ (***T***7~~10~~). See section 12.5.10 for instructions on reporting of pregnancies.

The time period for collecting and recording of AESIs will begin at the first receipt of study vaccines and will end ***6***~~12~~ months following administration of the study vaccines (***Day 361***~~541~~ (***T***7~~10~~). See section 12.5.10.5 for instructions on reporting of AESIs.

Section 12.5.9.3.2 Assessment of adverse events / Assessment of intensity

The maximum intensity of local ***I***~~i~~njection Site Induration, Swelling, Erythema (redness) will be scored at GSK as follows:

Section 12.5.9.3.2 Assessment of adverse events / Assessment of causality

All solicited ***local and systemic***~~local (injection site)~~ AEs will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Section 12.5.9.4 Recording of AEs related to COVID-19

For COVID-19 infection-related AEs, sites should follow routine AE/SAE processes as outlined in the protocol, using the following terms according to WHO defined case definitions:

- ***Suspected COVID-19 case***
- ***Probable COVID-19 case***
- ***Confirmed COVID-19 case [WHO, 2020]***

12.5.9.4.1 WHO Case Definition

- ***Suspected COVID-19 case***

  A. A person who meets the clinical AND epidemiological criteria

  Clinical criteria:

  Acute onset of fever AND cough OR acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status

  AND

  Epidemiological criteria:

  Residing or working in an area with high risk of transmission of virus: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; anytime within the 14 days prior to symptom onset OR residing to travel to an area with community transmission anytime within the 14 days prior to symptom onset OR working in any health care setting, including within health facilities or within the community; anytime within the 14 days prior to symptom onset

  OR

  B. A patient with severe acute respiratory illness (SARI: acute respiratory infection with history of fever or measured fever of ≥38.0°C, and cough; with onset within the last 10 days; and requires hospitalization)

- ***Probable COVID-19 case***

  A. A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or epidemiologically linked to a cluster with at least one confirmed case

  OR

  B. A suspect case with chest imaging showing findings suggestive of COVID-19 disease*

  **** Typical chest imaging findings suggestive of COVID-19 include the following:***

  Chest radiography: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution

  Chest computed tomography (CT): multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution

  Lung ultrasound: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms

  OR

  C. A person with recent anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause.

  OR

D. Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or epidemiologically linked to a cluster with at least one confirmed case.

- ***Confirmed COVID-19 case***

  A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms. See "Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases" [WHO, 2019] for details.

Section 12.5.10.3 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 ***or email*** it to the Study Contact for Reporting SAEs (refer to the SPONSOR INFORMATION) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

Section 12.5.11. Updating of SAE, pregnancy, and AESI information after removal of write access to the subject's eCRF

When additional SAE or 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 ***or emailed*** to the Study Contact for Reporting SAEs (refer to the SPONSOR INFORMATION) or to GSK Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

Section 12.5.12.2 Post-vaccination Visit(s)

Post-vaccination visits or calls will be performed on Day 15, 75, 121, 195, 241, 301, ***and 361***~~, 421, 481 and 541~~.

Section12.6.2 Contraception guidance

Table 29 Highly Effective Contraceptive Methods

Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable • ***oral***

12.8.1 Protocol amendment 2

Overall Rationale for the Amendment/Administrative change: This protocol has been amended as a consequence of feedback from Center for Biologics Evaluation and Research (CBER) [IND 14605 EOP2 Meeting - FDA's - V72_72 Endpoint Comments dated 11 October 2019]. The amendment has also implemented feedback from the Unites States (US) Institutional Review Board (IRB) on Protocol Amendment 1. In addition, the scope of this post-marketing commitment study has been extended to demonstrate the effectiveness, immunogenicity and safety of GSK's investigational combined

meningococcal ABCWY vaccine (from a phase III MenABCWY study) along with the rMenB+OMV NZ vaccine.

Section # and Name	Description of Change	Brief Rationale
In this amendment, there has been a major update to the study in terms of objectives and study design. Therefore, almost all sections in the protocol have been impacted by the change and suitable changes have been made everywhere. Amendment 1 to Amendment 2 track changes document contains all changes made to the protocol (Amendment 1). Brief rationale has been added, as applicable sections in the protocol track changes document (in a different colour). Please find below the Section number and name of the sections most impacted and where changes have been made:		
Section # and Name		
Title page		
1. Synopsis		
2. Schedule of activities		
3.1 Study rationale		
3,2 Background		
3.3 Benefit/Risk section		
3.3.1 Risk assessment		
3.3.2 Benefit assessment		
3.3.3 Overall Benefit: Risk conclusion		
4. Objectives and Endpoints		
5.1 Scientific Rationale for study design		
5.1.1. Rationale for use of placebo		
5.2 Overall design		
5.3 Number of subjects		
6.1. Inclusion criteria for enrolment		
6.2. Exclusion criteria for enrolment		
6.3. Criteria for temporary delay for enrolment and vaccination		
6.4 Screen and baseline failures		
7.1. Treatments administered		
7.1.1. Precautions to be observed in administering study vaccine		
7.1.2 Vaccine Administration Error or Overdose of Vaccine		
7.2 Method of treatment assignment		
7.2.1. Subject identification		
7.2.2.2.1 Study group and treatment number allocation		
7.2.3. Allocation of subjects to assay subsets		
7.2.3.1 Randomisation to strains for enc-hSBA testing		
7.3. Blinding and unblinding		
7.3.1 Emergency unblinding		
7.5.1. Recording of concomitant medications/products and concomitant vaccinations		
7.5.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses		
7.6 Intercurrent medical conditions that may lead to elimination of a subject from per-protocol analyses		
7.8 Warnings and precautions		
7.9 Treatment after completion of the study		
8 Study Assessments And Procedures		
8.2. Data collected from Subjects		
8.3.1 Screening/ Eligibility criteria		
8.3.2. Collection of demographic data		
8.3.4. General and symptom-directed physical examination		
8.3.5. Pregnancy test		
8.4 Effectiveness and/or immunogenicity assessments		

Section # and Name	Description of Change	Brief Rationale
8.4.2.1. Blood sampling for effectiveness and immunogenicity response assessments		
8.4.2.2. Other biological samples		
8.4.3. Laboratory assays		
8.4.4.1. Immunological read-outs		
8.4.5. Immunological correlates of protection		
8.5.2. Follow-up Clinic Visit(s)		
8.5.3. Safety Follow-up Calls		
8.5.4. Time period and frequency for collecting AE and serious adverse event (SAE) information		
8.5.6.1 Contact information for reporting of serious adverse events, AESIs and pregnancies		
8.8. Study Termination Visit/ Study Conclusion		
8.8.1. Early Termination Visit		
9.1. Discontinuation from the study		
10. Statistical considerations		
10.1. Sample size determination (whole section)		
10.2. Populations for analyses		
10.3.3. Primary effectiveness and immunogenicity analyses		
10.3.4. Secondary effectiveness and immunogenicity analyses		
10.3.5. Safety analyses		
11. References		
12.1.1. List of abbreviations		
12.1.12. Glossary of terms		
12.2. Appendix 2: Clinical Laboratory tests		
12.3 Appendix 3: Clinical laboratories		
12.4.2. Financial disclosure		
12.4.5.1 Responsibilities of the Investigator and IRB/IEC		
12.4.9 Data quality assurance		
12.5.3. Solicited adverse events		
12.5.4. Other solicited adverse events		
12.5.5 Unsolicited adverse events		
12.5.9. Detecting and recording adverse events, serious adverse events and pregnancies		
12.5.9.1 Post-vaccination reminders		
12.5.9.2. Time period for detecting and recording adverse events, serious adverse events and pregnancies		
12.5.9.3. Evaluation of adverse events and serious adverse events		
12.5.9.3.2 Assessment of adverse events		
12.6.2. Contraception guidance		
12.6.3. Collection of pregnancy information		

Detailed description of Protocol Amendment changes:

The changed text of the amendment is to be indicated in bold italics in the body of the protocol and the deleted text (strikethrough) and the changed text (bold italics) is to be provided here below. However, due to extensive changes to the protocol at Amendment 2, most of which are applicable throughout the document (ex: group names), the amended text has been presented in black bold italics only at the first instance. In rest of the document it is written in `the section/ table applicable font. Only major changes have been presented below (deletions in strike-throughs and additions in bold italics). All changes from Amendment 1 including deletions have been presented in the Amendment 2 track changes document.

Changes in contributing authors have been presented below:

- PPD ***and*** PPD ***Cont***, Clinical Research and Development Lead***s***
- PPD, Clinical and Epidemiology Project Leader
- PPD ~~***and***~~ PPD, Study Statistician ***for GSK***
- PPD ~~***and***~~ PPD, Lead Statistician***s***
- PPD ***and*** PPD **-** PPD, Oversight Data Manager***s***
- PPD, PPD ~~***and***~~ PPD, Clinical Trials Supply Manager
- PPD ~~***and***~~ PPD**,** Clinical Laboratory Sciences Read-Out Team Lead
- PPD ~~***and***~~ PPD, Clinical Laboratory Sciences Study Manager***s***
- PPD, SERM Safety Scientist
- ~~PPD, SERM Safety Physician~~
- PPD, PPD and PPD, Global Regulatory Affairs
- PPD ~~, US Regulatory Affairs and~~ PPD**, *US Agent – Global Regulatory Affairs***
- ~~PPD, Local Delivery Lead~~
- PPD**, *Across Country Expert - Local Delivery Lead***
- PPD, US Medical Affairs Lead
- PPD ~~***and***~~ PPD, Global Patents

The following changes have been applied throughout the document:

Phase: ~~Phase 3b~~ = ***Phase III***

Randomisation ratio: ~~1:1:1~~ = ***5:5:3:3:3:1***

Study groups: ~~3~~ ***6*** groups = ~~r~~MenB_0_2_6 group, ~~r~~MenB_0_6 group, ***ABCWY-1 group, ABCWY-2 group, ABCWY-3 group,*** ~~Control~~ ***ACWY*** group

Epochs have been deleted throughout:

~~Epoch 001: Starting at Visit 1 (Day 1) and ending at the post-vaccination 3 blood sampling visit (Visit 5; Day 211).~~

~~Epoch 002: Starting after post-vaccination 3 blood sampling visit (Visit 5; Day 211) and ending at SFU 10 (T10; 360 days post-vaccination 3; Day 541).~~

Indication: Indication of *Bexsero* is presented in Section 3.2 Background.

Study visit: An additional study visit has been added (at Month 1, Day 31) – Visit 2. So

Visit 1 (Day 1, Month 0), ***Visit 2 (Day 31, Month 1),*** Visit 3 (Day 61, Month 2), Visit 4 (Day 91, Month 3), Visit 5 (Day 181, Month 6), Visit 6 (Day 211, Month 7).

Formulations: Vaccine formulations have been updates as per the current Product Lifecycle Management (PLM) process.

Objectives and endpoints: All objectives and endpoints have been edited/ rewritten. For readability, the entire table is not written in black bold italics.

~~**Objectives**~~	~~**Endpoints**~~
~~**Primary**~~	
~~To assess the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series when compared to the Control Group in adolescent and young adult subjects.~~ ~~Criterion to demonstrate effectiveness of rMenB+OMV NZ vaccine: lower limit of the two-sided 95% confidence interval (CI) for vaccine effectiveness against a randomly selected strain panel between the rMenB+OMV NZ and the Control group is above 40%.~~	• ~~The percentage of subjects without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series. The percentages of subjects will be averaged across all strains.~~
~~The study is considered a success if the criterion to demonstrate effectiveness is met for at least one of the vaccination schedules.~~	
~~**Secondary**~~	
~~To assess the effectiveness of the rMenB+OMV NZ vaccine against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series, when compared to the Control Group in adolescent and young adult subjects.~~	• ~~The percentage of subjects without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination.~~
~~To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.~~	• ~~The percentage of serogroup B invasive disease strains killed using enc-hSBA in each subject, at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.~~
~~To assess the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination.~~	• ~~The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at one month after the 2-dose dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series.~~
~~To assess the immune response to rMenB+OMV NZ vaccine against *N. meningitidis* serogroup B test strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA), at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series, when compared to the Control Group.~~	~~The immune response to rMenB+OMV NZ vaccine will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B test strains as following:~~ • ~~The percentage of subjects with hSBA titers ≥ lower limit of quantitation (LLOQ) for each and all serogroup B test strains at baseline and at one~~

~~Objectives~~	~~Endpoints~~
	~~month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-M; 0-,6-M) vaccination series.~~ • ~~The percentage of subjects with fourfold increase in hSBA titers one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-M; 0-,6-M) vaccination series relative to baseline defined as:~~ – ~~If the baseline titer is <limit of detection (LOD), then post-vaccination titer should be ≥ 4x LOD or ≥LLOQ, whichever is greater~~ – ~~If the baseline titer is ≥LOD but <LLOQ, then post-vaccination titer should be ≥4x LLOQ~~ – ~~If the baseline titer is ≥LLOQ, then post-vaccination titer should be ≥ 4x the baseline titer~~ • ~~Geometric mean titers (GMTs) at baseline and at one month after the 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series and geometric mean ratios (GMRs) at one month after 2-dose (0-,2-M; 0-,6-M) and 3-dose (0-,2-,6-M) vaccination series as compared to the baseline.~~
~~To evaluate the safety and reactogenicity of the rMenB+OMV NZ and MenACWY vaccines in adolescent and young adult subjects.~~	• ~~The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events during the 7 days (including the day of vaccination) following vaccination at Day 1, Day 61 and Day 181.~~ • ~~The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 7 and the 30 days (including the day of vaccination) following vaccination at Day 1, Day 61 and Day 181.~~ • ~~The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period.~~

~~M = Month; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest~~

Objectives	***Endpoints***
Primary	
Vaccine effectiveness (Test-based): rMenB+OMV NZ ***To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when***	***The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US N. meningitidis serogroup B strains, at 1 month after the:*** • ***3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7)*** • ***2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and*** • ***2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3)***

Objectives	*Endpoints*
compared to 1 month after the MenACWY vaccination. ***<u>Criterion</u>*** ***Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:*** • ***MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)*** • ***MenB_0_6 and ACWY groups (for 0,6-months schedule),*** • ***MenB_0_2_6 and ACWY groups (for 0,2-months schedule)***	• ***1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1).***
<u>Effectiveness (Responder-based): rMenB+OMV NZ</u> ***To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series of the rMenB+OMV NZ.*** ***<u>Criterion:</u>*** ***LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:*** • ***MenB_0_2_6 group (for 0,2,6-months schedule)*** • ***MenB_0_6 group (for 0,6-months schedule),*** • ***MenB_0_2_6 group (for 0,2-months schedule)***	***The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the:*** • ***3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)*** • ***2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group),*** • ***2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)***
<u>The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Section 10.1 for details on continuing the evaluation.</u>	
<u>Lot-to-lot consistency: MenABCWY vaccine</u> ***To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W and Y at 1 month after last vaccination (0,6-months).*** ***<u>Criterion:</u>*** ***The two-sided 97.5% CIs^ for the ratio of hSBA GMTs of antibodies against serogroups A, C, W and Y are within the [0.5;2.0] equivalence interval for each pair of lots.***	***GMTs directed against serogroups A, C, W and Y for each lot (ABCWY-1 group, ABCWY-2 group, ABCWY-3 group) at 1 month after the last vaccination (Day 211, Month 7)***
<u>Immunological non-inferiority: MenABCWY vaccine vs. MenACWY vaccine</u> ***To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the MenACWY vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against N. meningitidis serogroups A, C, W and Y at 1 month after the last MenABCWY***	***The percentages of subjects with 4-fold rise* in hSBA titres against N. meningitidis serogroups A, C, W and Y at 1 month after the:*** • ***last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and***

Objectives	*Endpoints*
vaccination (0,6-months) and 1 month after the MenACWY vaccination. *<u>Criterion</u>:* *LL of the 2-sided 97.5% CI^ for the group difference in percentages of subjects achieving a 4-fold rise* in hSBA titres is above -10%.*	• *1 month after the MenACWY vaccination for the ACWY group (Day 31, Month 1)* *relative to baseline (Day 1, Month 0).*
<u>Vaccine effectiveness (Test-based): MenABCWY vaccine</u> *To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0,6-months) when compared to 1 month after the MenACWY vaccination.* *<u>Criterion</u>:* *LL of the two-sided 97.5% CI^ for vaccine effectiveness is above 65% against a randomly selected strain panel between the ABCWY group (pooled lots) and the ACWY group.*	*The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US N. meningitidis serogroup B strains, at 1 month after the:* • *last vaccination for the ABCWY group (pooled) (Day 211, Month 7), and* • *1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).*
<u>Effectiveness non-inferiority: MenABCWY vaccine vs. rMenB+OMV NZ vaccine</u> *To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0,6-months schedule) compared to the rMenB+OMV NZ vaccine (0,2,6-months or 0,6-months or 0,2-months)† in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains.* *<u>Criterion</u>:* *LL of the two-sided 97.5% CI^ for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains is above -5% at 1 month after:* • *the last vaccination in ABCWY group (pooled lots) (for 0,6 months schedule), and* • *The last vaccination in MenB_0_2_6 group (for 0,2,6-months schedule) or the last vaccination in MenB_0_6 group (for 0,6-months schedule) or the second vaccination in MenB_0_2_6 group (for 0,2-months schedule*	*The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic US N. meningitidis serogroup B strains at 1 month after the:* • *last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and* • *3-dose vaccination series of rMenB+OMV vaccine (Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)†*
<u>Effectiveness (Responder-based): MenABCWY vaccine</u> *To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-*	*The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7).*

Objectives	*Endpoints*
hSBA at 1 month after the last vaccination of MenABCWY (0,6-months). ***<u>Criterion:</u>*** ***LL of the two-sided 97.5% CI^ for the percentages of subjects whose sera kill ≥70% of strains tested for MenABCWY is above 65%.***	
<u>Safety</u> ***To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY vaccines***	• ***The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.*** • ***The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.*** • ***The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 18].***
Secondary	
To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared to the rMenB+OMV NZ vaccine as measured by the percentages of subjects achieving a 4-fold rise in hSBA titres against N. meningitidis serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0,6-months schedule) and 1 month after the rMenB+OMV NZ vaccination (0,2,6-months or 0,6-months or 0,2-months)† ***<u>Criterion:</u>*** ***Non-inferiority will be demonstrated if the LL of the 2-sided 95% CI for the group difference in percentage of subjects achieving a 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains is above -10%.***	***The percentages of subjects with 4-fold rise** in hSBA titres against N. meningitidis serogroup B indicator strains at 1 month after the:*** • ***last MenABCWY vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and*** • ***3-dose vaccination series of rMenB+OMV vaccine(Day 211, Month 7 in MenB_0_2_6 group) or 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) or 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) †*** ***relative to baseline (Day 1, Month 0).***
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US N. meningitidis serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6	***The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US N. meningitidis serogroup B strains at 1 month after the:*** • ***3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)***

Objectives	*Endpoints*
group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	• *2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group)* • *2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)* • *last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and* • *MenACWY vaccination (Day 31, Month 1 in ACWY group).*
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	*The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the:* • *3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)* • *2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group)* • *2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and* • *last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)*
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against N. meningitidis serogroup B indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	*The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against N. meningitidis serogroup B indicator strains as following:* *1. The percentages of subjects with hSBA titres ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:* • *3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)* • *2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group)* • *2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and* • *last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)* *2. The percentages of subjects with 4-fold rise** in hSBA titres at 1 month after the:* • *3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)* • *2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group)* • *2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and* • *last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)* *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:* • *3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)* • *2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group)*

Objectives	*Endpoints*
	• *2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and* • *last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)* *4. hSBA GMRs at 1 month after the:* • *3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group)* • *2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group)* • *2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and* • *last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)* *relative to the baseline (Day 1, Month 0).*
To assess the immune response to MenABCWY (0,6-months schedule) and MenACWY (single dose) vaccines against N. meningitidis serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and at 1 month after the first and the last MenABCWY vaccination and 1 month after the MenACWY vaccination.	*1. The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • *at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and* • *at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).* *2. The percentage of subjects with 4-fold rise* in hSBA titres at 1 month after the:* • *first vaccination (Day 31, Month 1) for the ABCWY group (pooled lots) compared to the MenACWY vaccination in the ACWY group (Day 31, Month 1)* *relative to baseline (Day 1, Month 0).* *3. hSBA GMTs against N. meningitidis serogroups A, C, W and Y at baseline (Day 1, Month 0) and:* • *at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and* • *at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).* *4. hSBA GMRs against N. meningitidis serogroups A, C, W and Y at:* • *1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots) as compared to baseline (Day 1, Month 0), and* • *1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0).* *5.The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at baseline (Day 1, Month 0) and:*

Objectives	*Endpoints*
	• ***at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the ABCWY group (pooled lots), and*** • ***at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).***

Abbreviations: ELISA = enzyme-linked immunosorbent assay; Enc-hSBA = endogenous complement human serum bactericidal assay; GMC = geometric mean concentrations; GMT = geometric mean titre; GMR = geometric mean ratio; CI = confidence interval; hSBA = human serum bactericidal assay; LOD: limit of detection; LLOQ = lower limit of quantitation; LL = lower limit; AE = Adverse event; SAE = Serious adverse event; AESI = Adverse event of special interest

N.meningitidis serogroup B indicator strains = M14459, 96217, M07-0241084 and NZ98/254 for fHbp, NadA, NHBA and PorA P1.4 antigens, respectively. The NHBA indicator strain may be subject to change during the study, before clinical testing starts. In this case, this change will be documented either in a protocol amendment or in the clinical report.

Refer to Section 10 for details on evaluation of objectives and sample size justification. Refer to Glossary of terms for definitions of test-based and responder-based effectiveness

^ If the co-primary effectiveness objectives for rMenB+OMV NZ are met, then all objectives for MenABCWY will be evaluated at 95% CI. Refer to Section 10.1 for details

† If all objectives of rMenB+OMV NZ are met, the comparator will be the 0,2-months schedule. If the 0,2-months objective is not met, and the 0,6-months is met, then the 0,6-months schedule will be the comparator. If the 0,6-months is also not met, then the 0,2,6-months schedule will be the comparator.

****For the Men A, C, W, Y evaluation, the 4-fold rise is defined as:***

- ***a post-vaccination hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4***
- ***a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and***
- ***a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.***

*****For the MenB evaluation, the 4-fold rise per each indicator strain is defined as:***

- ***a post-vaccination‡ hSBA titre ≥16 for subjects with a pre-vaccination hSBA titre <4***
- ***a post-vaccination‡ hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and***
- ***a post-vaccination‡ hSBA titre ≥4 times the pre-vaccination hSBA titre for subjects with a pre-vaccination hSBA titre ≥ LLOQ***

‡ = post-2nd vaccination for 0,6 and 0,2 schedule and post-3rd vaccination for 0,2,6 schedule)

Entire statistical section (Section 10) has been rewritten in line with the current objectives and endpoints.

The following section has been deleted as it is not applicable for this study (no information will be collected from any male subject's female partners who become pregnant while the male subject is participating in this study):

12.6.3.1 Male subjects with partners who become pregnant

- ~~Investigator will attempt to collect pregnancy information on any male subject's female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.~~
- ~~After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the~~

~~appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.~~

- ~~Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK~~
- ~~Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.~~
- ~~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.~~

12.8.1 Protocol amendment 1

Overall Rationale for the Amendment/Administrative change: As per the recommendation from Center for Biologics Evaluation and Research (CBER) [IND 11561 Amendments 257, 283 – CBER comments on Study Protocol V72_72 Version 1, dated February 08, 2019], the scope of the study has been extended to include the 3-dose (0-,2-,6-month) schedule and an additional 2-dose schedule (0-,6-month) along with the 2-dose (0-,2-month) schedule planned originally. The study will assess the immunogenicity of the 2-dose and 3-doses vaccination with rMenB+OMV NZ vaccine along with effectiveness and safety.

Section # and Name	Description of Change	Brief Rationale
Title page	EudraCT number is added	This study is in scope of EudraCT
	The company name is added to the Title	In line with posting requirements
In this amendment, there has been a major update to the study design in terms of study groups, vaccinations given, time points etc. The objectives and endpoints have been updated as well. Therefore, almost all sections in the protocol have been impacted by the change and suitable changes have been made everywhere. Please find below the Section number and name of the sections most impacted and where changes have been made:		
Section # and Name		
1. Synopsis		
2. Schedule of activities		
3.1 Study rationale		
3,2 Background		
3.3 Benefit/Risk section		
4. Objectives and Endpoints		
5.1. Scientific Rationale for study design		
5.1.1. Rationale for use of placebo		
5.2.Overall design		
5.3. Number of subjects		
5.4. Subject and study completion		
6.1. Inclusion criteria for enrolment		
6.2. Exclusion criteria for enrolment		
6.3. Criteria for temporary delay for enrolment and vaccination		
7.1. Treatments administered		
7.1.1. Precautions to be observed in administering study vaccine		
7.2.1. Subject identification		

Section # and Name	Description of Change	Brief Rationale
7.2.2. Randomisation of treatment		
7.2.3. Allocation of subjects to assay subsets		
7.3. Blinding and unblinding		
7.5.1. Recording of concomitant medications/products and concomitant vaccinations		
7.5.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses		
8.2. Data collected from Subjects		
8.3.2. Collection of demographic data		
8.3.4. General and symptom-directed physical examination		
8.3.6. Pre-vaccination body temperature		
8.4. Effectiveness and/or immunogenicity assessments		
8.4.2. Biological samples		
8.4.3. Laboratory assays		
8.5.2. Follow-up Clinic Visit(s)		
8.5.3. Safety Follow-up Calls		
8.5.7. Follow-up of AEs and SAEs		
8.8. Study Termination Visit/ Study Conclusion		
8.8.1. Early Termination Visit		
10.1. Sample size determination		
10.2. Populations for analyses		
10.3.2. Demography and baseline characteristics analyses		
10.3.3. Effectiveness analyses		
10.3.4. Immunogenicity analyses		
10.3.5. Safety analyses		
11. References		
12.1.1. List of abbreviations		
12.1.12. Glossary of terms		
12.2. Appendix 2: Clinical Laboratory tests		
12.5.3. Solicited adverse events		
12.5.6. Adverse events of special interest		
12.5.9. Detecting and recording adverse events, serious adverse events and pregnancies		
12.5.12. Follow-up of adverse events, serious adverse events, and pregnancies		

Detailed description of Protocol Amendment changes: As per process, the changed text of the amendment change should be indicated in bold italics in the body of the protocol. The deleted text (strikethrough) and the changed text (bold italics) is to be provided in this appendix. However due to the extensive nature of this amendment, the changes in the body of the protocol are indicated in the bold italics only at one instance. In this section, explanation has been provided for the changes done throughout the document. The track changes document can be referred to see all the changes made to the protocol (at Amendment 1).

Other changes: As the sponsorship of the study has changed from Novartis Vaccines to GlaxoSmithKline Biologicals' (GSK), the protocol has been transcribed to the GSK's protocol template (DS-BIO-CLIN-1000 vs 16.1). All applicable & mandatory sections and text have been included during the template transfer without highlighting the changes. Table 2 and Section 12.9 only present the rationale and the changes made to the protocol amendment.

Signature Page for 205416 TMF-12466267 v1.0

Reason for signing: Approved	Name: PPD Role: A Date of signature: 12-May-2021 13:02:15 GMT+0000

Signature Page for TMF-12466267 v1.0