Protocol Amendment 3

Study ID: 213171

Official Title of the Study: A phase IIIB, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of GSK's meningococcal ABCWY vaccine when administered in healthy adolescents and adults, previously primed with meningococcal ACWY vaccine.

NCT Number: NCT04707391

Date of Document: 2 November 2021

TITLE PAGE

Protocol Title: A phase IIIB, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of GSK's meningococcal ABCWY vaccine when administered in healthy adolescents and adults, previously primed with meningococcal ACWY vaccine

Protocol Number: 213171 (MENABCWY-019)

Amendment Number: 3

Product: GlaxoSmithKline Biologicals (GSK)'s combined Meningococcal Groups A, B, C, W, and Y vaccine (GSK3536819A)

Short Title: Immunogenicity and safety study of GSK's MenABCWY vaccine in healthy adolescents and adults previously primed with MenACWY vaccine

Study Phase: IIIB

Sponsor Name: GlaxoSmithKline Biologicals SA

Legal Registered Address: Rue de l'Institut, 89, 1330 Rixensart, Belgium

IND Number: BB-IND-014605

EudraCT Number: 2019-004982-42

Date of Protocol Amendment: 1 November 2021

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

PPD

November 2, 2021

Daniela Toneatto, MD
Clinical and Epidemiology R&D Project Lead

Date

Refer to the study reference manual for Medical Monitor name and contact information.

PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES

Table 1 Document History

Document	Date	Substantial	Region
Amendment 3	01 Nov 2021	Yes	Global
Amendment 2	12 Feb 2021	Yes	Global
Amendment 1	31 Aug 2020	No	Global
Original Protocol	04 Jun 2020	-	-

The summary of changes in protocol amendments 1 and 2 is provided in Appendix 7.

Amendment 3 – 1 November 2021

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 3:

The primary goals of this amendment are:

1. To extend the window for the priming MenACWY vaccination prior to enrollment from 4 to 6 years to at least 4 years. This is to increase the pool of potential participants who may benefit from the intervention.
2. To allow for interim analyses of immunological objectives after all participants have completed Visit 4, and of safety objectives after at least 50% of participants have completed Visit 4.
3. Other minor changes include the timing for reporting pregnancies and the change of the reference N MenB NHBA strain.

The detailed changes and the rationale for the changes are presented in Table 2.

Table 2 Description of Changes in Amendment 3

Section # and Name	Description of Change	Brief rationale
Substantial Changes		
1.1 Synopsis **8.1.2 Laboratory Assays** – Table 10 **8.1.3 Immunological Read-outs –** Table 11, footnotes **9.4.4.2 Immune Response – *N. Meningitidis* Serogroup B Indicator Strains (Measured by hSBA)** **9.4.5.1 Immune Response – *N. Meningitidis* Serogroup B Indicator Strains (Measured by hSBA)** **Appendix 3 Clinical Laboratory Tests**	The NHBA indicator strain M07-0241084 was replaced by M13520. All instances in the text where the M07-0241084 was used were revised for M13520.	Assay format using M13520 as NHBA indicator strain has been recently validated for use in clinical studies.
1.3 Schedule of Activities – Table 3	The double-border line was added after Visit 4 (Day 211), and the following footnote was added: The double-line border following D211 indicates the analyses which will be performed on all data (i.e., the data that are as clean as possible) obtained up to D211.	To indicate the time point for the interim analysis.

Section # and Name	Description of Change	Brief rationale
	The visit window for the telephone contacts 2 and 4 (i.e., T2 and T3) was changed from −5/+14 to −3/+3 days.	To correct the error.
4.2 Scientific Rationale for Study Design	The following change was made (the new text is **bold** and the deleted text is ~~strikethrough~~): Given the aim of the study is to evaluate the MenABCWY booster response in healthy participants previously primed with MenACWY vaccine, eligible participants must have received a previous vaccination with a quadrivalent meningococcal conjugate vaccine (MenACWY; *Menveo* or *Menactra*) at least 4 years prior to study start.	To reflect the change in the time period for a previous vaccination to allow inclusion of a broader population.
5.1 Inclusion Criteria	The following criterion's text was revised as follows (the new text is **bold** and the deleted text is ~~strikethrough~~): 4. Previous vaccination with 1 dose of MenACWY vaccine at an age of 10 years or older, with an interval of at least 4 between the previous MenACWY vaccine and enrollment (informed consent and assent [as applicable]) into this study.	To allow enrollment of a broader population.

Section # and Name	Description of Change	Brief rationale
8.1.2 Laboratory Assays - Table 10, footnotes **8.1.3 Immunological Read-outs – Table 11, footnotes** **Appendix 3 Clinical Laboratory Tests**	The following text was removed: The NHBA M07-0241084 indicator strain may be subject to change to an alternative NHBA indicator strain (e.g., strain M13520) during the study. In this case, this change will be documented either in a protocol amendment or in the CSR.	Because hSBA using NHBA strain M13520 has been recently validated.
8.1.2 Laboratory Assays – Table 10 footnotes	The following footnote was removed: [1] Strain(s) and unit(s) might be subject to change during the study (e.g., in case of requalification, revalidation or standardization). In this case, this will be documented either in a protocol amendment or in the clinical report. The remaining 2 footnotes shifted accordingly.	The footnote is no longer necessary considering the documented change in the strain.
8.3.6.4 Regulatory Reporting Requirements for SAEs – Table 13	The following footnote was revised as follows (the new text is **bold** and the deleted text is ~~strikethrough~~): ~~3~~[2] ELISA 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.~~**and submitted prior to the submission of the clinical study report.**	Because any change on assay format will be first submitted and endorsed with Health Authorities.

Section # and Name	Description of Change	Brief rationale
9.1 Statistical Hypotheses	The following introduction was added: The following study hypotheses are ordered into 2 families that will be tested in a fixed sequential design with full alpha propagation. Family 1 will be tested first and family 2 will only be tested if the hypothesis in family one is successfully demonstrated.	For added clarity.
9.4.1 General Considerations	The following change was made: Fixed sequential testing with full alpha propagation in pre-ordered hypotheses families (Family 1 and Family 2, as defined in Section 9.1) will be applied. The assay cut-off values will be defined by the laboratory before analysis and will be documented in a protocol amendment~~or in the clinical study report~~.	For accuracy.
9.4.3.1 Immunological Non-inferiority of MenABCWY vs. MenACWY	The following sentence was added: A sensitivity analysis including minimization factors as covariates will be performed using a logistic model and will be detailed in the SAP.	To add the details on the sensitivity analysis.

Section # and Name	Description of Change	Brief rationale
9.4.4.2 Immune Response – *N. Meningitidis* Serogroup B Indicator Strains (Measured by hSBA) **9.4.5.1Immune Response – *N. Meningitidis* Serogroup B Indicator Strains (Measured by hSBA*)***	The following phrase was removed: **Note: Strains and unit(s) might be subject to change during the study (e.g., in case of requalification, revalidation or standardization). In this case, this will be documented either in a protocol amendment or in the CSR.*	It is no longer necessary because the change in the strain has been documented in the protocol.
9.5 Interim Analyses	The following text was added: An interim analysis of safety objectives may be conducted after at least 50% of participants have completed Visit 4. An interim analysis of immunological objectives may also be performed after all participants have completed Visit 4. If performed, the assessment of the primary immunological objectives will follow the order described in Section 9.4.3.1 with analysis of family 1 preceding that of family 2.	To add details concerning the addition of the interim analysis after Visit 4.
9.5.1 Sequence of Analyses	The phrase "Not applicable" was removed. The following text was added: The interim analysis for the evaluation of the co-primary objectives will respect the hierarchical order described in Section 9.4.3.1.	To reflect the addition of the interim analysis.

Section # and Name	Description of Change	Brief rationale
9.5.2 Statistical Consideration for Interim Analysis	The phrase "Not applicable" was removed. The following text was added: No changes in statistical methodology for the immunological and safety objectives are foreseen compared to what is planned for the final analysis. Data for the interim analysis may be analyzed by an independent unblinded group; if so, only group unblinded results will be presented.	For clarity.
Administrative Changes		
Title Page	*Original text:* Amendment Number: Amendment 2 *New Text:* Amendment Number: 3 *Original date:* 12 February 2021 *New date:* 1 November 2021	To reflect the change in the protocol version.
Page Headers	*Original text:* Protocol 213171 (MENABCWY-019) – Amendment 2 *New text:* Protocol 213171 (MENABCWY-019) – Amendment 3	To reflect the change in the protocol version.

Section # and Name	Description of Change	Brief rationale
Protocol Amendment Summary of Changes	The summary of changes for Protocol Amendment 3 was added to this section. The summary of changes for Protocol Amendment 2 was transferred from this section to a newly added Appendix 7. The document history was updated.	To present the most recent summary of changes and the protocol history.
Appendix 7 Protocol Amendment History	The new appendix was added to include the summaries of changes for the previous 2 protocol amendments (1 and 2)	To restructure the content for better readability.
Appendix 8 Signature of Investigator	Originally Appendix 7. Changed to Appendix 8.	Because the new Appendix 7 was added.
	Original text: VERSION: Amendment 2 *New text:* VERSION: Amendment 3	To reflect the change in the protocol version.
Additional administrative changes	Page numbers, Table of Contents, Table of Tables were updated. Table numbering shifted. Relevant editorial changes were also made (e.g., internal cross-references, formatting).	Updates were made according to the changes in the content of the document.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase IIIB, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of GSK's meningococcal ABCWY vaccine when administered in healthy adolescents and adults, previously primed with meningococcal ACWY vaccine

Short Title: Immunogenicity and safety study of GSK's MenABCWY vaccine in healthy adolescents and adults previously primed with MenACWY vaccine

Rationale: GlaxoSmithKline Biologicals SA (GSK) is developing a combination vaccine intended to protect against 5 of the most prevalent serogroups of *Neisseria meningitidis* (*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.

The investigational MenABCWY combination vaccine is based upon 2 established GSK vaccines, the quadrivalent meningococcal ACWY (MenACWY) conjugate vaccine (*Menveo*) and the multi-component recombinant meningococcal B (MenB) vaccine (*Bexsero*).

The United States (US) Advisory Committee on Immunization Practices (ACIP) recommends vaccination with a quadrivalent conjugated meningococcal vaccine for adolescents at 11 to 12 years of age with a booster dose at 16 years of age, based on the data showing a robust immune response to a booster dose of MenACWY vaccines in this age group. The ACIP also recommends MenB vaccination in persons aged 10 years and older who are at increased risk for MenB disease and in adolescents and young adults aged 16 to 23 years not at increased risk based on shared clinical decision making.

Based on the current ACIP recommendations for a MenACWY booster dose at 16 years of age and for MenB vaccination at 16 to 23 years of age, there is a need to evaluate the response to the MenABCWY vaccine in MenACWY-vaccine primed individuals. In the context of the MenABCWY investigational vaccine development, the MenACWY booster response has been evaluated in 2 phase II clinical studies (Sáez-Llorens, 2018; Szenborn, 2018). Although the sample size of these studies was small, a robust anamnestic immune response against A, C, W, and Y serogroups was demonstrated at 1 month after the administration of the first dose of the MenABCWY vaccine in participants previously primed with the GSK MenACWY vaccine.

The main purpose of this phase IIIB clinical study is to assess the immunogenicity and safety of the MenABCWY vaccine when administered as a booster in healthy adolescents and young adults, previously primed with a MenACWY vaccine.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 1) To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the second MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	• The percentages of participants with a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the second vaccination for the ABCWY group (Day 211, Month 7), and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 2) To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the first MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	• The percentages of participants with a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the first vaccination for the ABCWY group (Day 31, Month 1), and 1 month after the single dose of MenACWY vaccination for the ACWY group (Day 31, Month 1), relative to baseline (Day 1, Month 0).
Safety To evaluate the safety and reactogenicity of the MenABCWY and MenACWY vaccines.	• The frequencies and percentages of participants with solicited administration site events (i.e., injection site pain, erythema, swelling, induration) and solicited systemic events (i.e., fever [body temperature ≥38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) during the 7 days (including the day of vaccination) following vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group). • The frequencies and percentages of participants 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 vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group).

Objectives	Endpoints
	• The percentages of participants with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period (Month 0 to Month 12).
Secondary	
To assess the immune response to MenABCWY (0,6-month schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W, and Y, at pre-vaccination and at 1 month after the first and last MenABCWY vaccinations and 1 month after the MenACWY vaccination.	• The percentages of participants with hSBA titers ≥Lower Limit of Quantitation (LLOQ) 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, and – at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1). • The geometric mean titers (GMTs) 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 (Day 211, Month 7) vaccinations for the ABCWY group, and – at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1). • The geometric mean ratios (GMRs) against serogroups A, C, W, and Y: – at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group as compared to baseline (Day 1, Month 0) and – at 1 month after the MenACWY vaccination (Day 31, Month 1) for the ACWY group as compared to baseline (Day 1, Month 0).
To assess the immune response to the MenABCWY vaccine (0,6-month schedule) against *N. meningitidis* serogroup B indicator strains, at pre-vaccination and at 1 month after the last MenABCWY vaccination.	• The percentages of participants with hSBA titers ≥LLOQ for each and all serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the last vaccination (Day 211, Month 7) for the ABCWY group.

Objectives	Endpoints
	• The percentages of participants with 4-fold rise[1] in hSBA titers against each *N. meningitidis* serogroup B indicator strains at 1 month after the last vaccination (Day 211, Month 7) relative to baseline (Day 1, Month 0) for the ABCWY group. • GMTs against each serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the last vaccination (Day 211, Month 7) for the ABCWY group. • GMRs against each serogroup B indicator strains at 1 month after the last vaccination (Day 211, Month 7) as compared to the baseline (Day 1, Month 0) for the ABCWY group.
CCI [redacted]	

AESI = adverse event of special interest; CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentration; GMT = geometric mean titer; GMR = geometric mean ratio; hSBA = human serum bactericidal assay; LLOQ = lower limit of quantitation; *N. meningitidis* = *Neisseria meningitidis*; SAE = serious adverse event

[1] Refer to Section 9.0 for the (seroresponse) definition of the 4-fold rise.

CCI

[redacted]

Overall Design:

This is a phase IIIB, randomized, controlled, observer-blind, multi-centric study with 2 parallel study groups of healthy adolescents and young adults aged 15 to 25 years (i.e, 25 years + 364 days). The participants will be randomized at a 1:1 ratio to the ABCWY or ACWY group using an Interactive Voice Response System randomization.

Number of Participants:

Approximately 1206 participants will be randomly assigned to study intervention or placebo for an estimated total of 1084 evaluable participants or 542 evaluable participants per study group.

For more information, see Section 9.0, Statistical Considerations, and Section 9.2, Sample Size Determination.

Study Groups:

- **ABCWY:** 603 participants will receive 2 doses of the MenABCWY vaccine at Visit 1 (Day 1) and Visit 3 (Day 181) (0,6-month schedule) and 1 dose of placebo at Visit 4 (Day 211).
- **ACWY:** 603 participants will receive 1 dose of MenACWY vaccine at Visit 1 (Day 1) (single dose) and 2 doses of MenB vaccine at Visit 3 (Day 181) and Visit 4 (Day 211).

Duration: The total duration of the study, per participant, will be approximately 12 months (4 visits), including 6 months of Extended Safety Follow-Up (ESFU) period after the last dose of investigational vaccine (Visit 3, Day 181).

Statistical Methods:

Immunological non-inferiority: MenABCWY vs. MenACWY

Non-inferiority will be demonstrated if, the lower limit of 2-sided 95% confidence interval (CI) for the percent difference in 4-fold rise in human serum bactericidal assay (hSBA) titers (p_MenABCWY − p_MenACWY) is above −10%, for each serogroup A, C, W, and Y. For each of the serogroups A, C, W, and Y, the percentages of participants with 4-fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each study group at time point of interest. The standardized asymptotic CIs between group differences in percentages will be derived using the method of Miettinen and Nurminen method (Miettinen, 1985).

Immune response to MenABCWY and MenACWY against serogroups A, C, W, and Y

Immune response of MenABCWY and MenACWY against A, C, W and Y serogroups will be evaluated from the percentages of participants with hSBA titers ≥lower limit of quantitation (LLOQ) for each of the 4 serogroups. The corresponding exact 2-sided 95% CIs based on

Clopper-Pearson method will be calculated for each study group, each serogroup and at each time point (baseline/pre-vaccination, 1 month after first vaccination and 1 month after last vaccination). Geometric mean titers (GMTs) and Geometric mean ratios (GMRs) (post-vaccination/baseline titer), and their associated 2-sided 95% CIs will be computed for each study group, for each serogroup and at each time point.

Immune response to MenABCWY against Men B indicator stains

Immune response of MenABCWY against each and all of the 4 Men B indicator strains (M14459, M13520, 96217 and NZ98/254) will be evaluated from the percentages of participants with hSBA titers ≥LLOQ and from the percentages of participants with 4-fold rise for each of the 4 Men B indicator strains. The corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each and all Men B indicator strains, at baseline/pre-vaccination and 1 month after last vaccination, and separately for 1 month after the first vaccination.

Geometric mean titers and GMRs (post-vaccination/baseline titer), and their associated 2-sided 95% CIs will be computed for each Men B indicator strain, at baseline/pre-vaccination and 1 month after last vaccination, and separately for 1 month after the first vaccination.

Safety

The frequencies and percentages of participants will be presented for:

- solicited administration site and systemic adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1 and Day 181
- unsolicited AEs during the 7 and the 30 days (including the day of vaccination) following vaccination at Day 1 and Day 181
- serious AEs, AEs leading to withdrawal, AEs of special interest and medically attended AEs throughout the study period (Day 1 to Day 361)

Data Monitoring Committee: No.

See Appendix 1, Glossary of Terms, for the definitions of randomization, Interactive Voice Response System, investigator, participants, evaluable participants, solicited and unsolicited AEs.

1.2 Schema

This is a phase IIIB, randomized, controlled, observer-blind, multi-centric study with 2 parallel groups (see Figure 1). A total of 1206 participants will be randomized in a 1:1 ratio as follows:

- **ABCWY**: 603 participants will receive 2 doses of the MenABCWY vaccine at Day 1 and Day 181 (0,6-months schedule) and 1 dose of placebo at Day 211.
- **ACWY**: 603 participants will receive 1 dose of MenACWY vaccine at Day 1 (single dose) and 2 doses of MenB vaccine at Day 181 and Day 211.

1.3 Schedule of Activities

Table 3 Schedule of Activities

Age	**15 to 25 Years (25 Years + 364 Days) at Study Start**								
Type of contact	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**PC**
Visit/phone contact[1]	**V1**	**T1**	**V2**	**T2**	**V3**	**T3**	**V4**	**T4**	**T5**
Time points	**D1 M0**	**D15**	**D31 M1**	**D91 M3**	**D181 M6**	**D195**	**D211 M7**	**D271 M9**	**D361 (ESFU)**
Visit window (days)	**n/a**	**(−3/+3)**	**(−5/+14)**	**(−3/+3)**	**(−5/+14)**	**(−3 /+3)**	**(−5/+14)**	**(−3/+3)**	**(−7/+21)**
Days post-vaccination[2]	**0**	**14 post-vacc 1**	**30 post-vacc 1**	**90 post-vacc 1**	**180 post-vacc 1**	**14 post-vacc 2**	**30 post-vacc 2**	**90 post-vacc 2**	**180 post-vacc 2**
Sampling time points	**pre-vacc**		**post-vacc 1**				**post-vacc 2**		
Informed consent and Informed assent (as applicable)[3]	●[4]								
Check inclusion/exclusion criteria[5]	●[4]				○[4]		○[4]		
Collect demographic data	●[4]								
Vaccine(s)/product									
Study group and treatment number allocation	○[4]								
Treatment number allocation for subsequent doses					○		○		
Recording of administered treatment number	●				●		●		
Vaccine/Product administration	●				●		●		
Post-injection assessment (30 minutes)[6, 11]	●				●		○		
Laboratory assays									
Blood sampling (approximately 20 mL)[7]	●[4]		●[4]				●[4]		
Safety assessments									
Medical history	●[4]								

Age	**15 to 25 Years (25 Years + 364 Days) at Study Start**								
Type of contact	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**PC**
Visit/phone contact[1]	**V1**	**T1**	**V2**	**T2**	**V3**	**T3**	**V4**	**T4**	**T5**
Time points	**D1 M0**	**D15**	**D31 M1**	**D91 M3**	**D181 M6**	**D195**	**D211 M7**	**D271 M9**	**D361 (ESFU)**
Visit window (days)	**n/a**	**(−3/+3)**	**(−5/+14)**	**(−3/+3)**	**(−5/+14)**	**(−3 /+3)**	**(−5/+14)**	**(−3/+3)**	**(−7/+21)**
Days post-vaccination[2]	**0**	**14 post-vacc 1**	**30 post-vacc 1**	**90 post-vacc 1**	**180 post-vacc 1**	**14 post-vacc 2**	**30 post-vacc 2**	**90 post-vacc 2**	**180 post-vacc 2**
Sampling time points	**pre-vacc**		**post-vacc 1**				**post-vacc 2**		
General physical examination[9]	○[4]								
Symptom-directed physical examination			○		○[4]		○[4]		
Urine pregnancy test for females of childbearing potential[10]	●[4]				●[4]		●[4]		
Check criteria for temporary delay for enrollment and vaccination and/or blood sampling	○[4]		○		○[4]		○[4]		
Check contraindications and warnings and precautions to vaccination	○[4]				○[4]		○[4]		
Pre-vaccination body temperature[11]	●[4]				●[4]		●[4]		
Record any concomitant medication/vaccination	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions	●	●	●	●	●	●	●	●	●
Training and distribution of eDiaries	○				○				
Recording of solicited events (Days 1-7 post-vaccination) in eDiary	×				×				
Recording of unsolicited adverse events (Days 1-30 post-vaccination)	●	●	●		●	●	●		
Return and review of eDiaries			○				○		
Recording of any AEs leading to vaccine/study withdrawal[8]	●	●	●	●	●	●	●	●	●

Age	**15 to 25 Years (25 Years + 364 Days) at Study Start**								
Type of contact	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**Visit**	**PC**	**PC**
Visit/phone contact[1]	**V1**	**T1**	**V2**	**T2**	**V3**	**T3**	**V4**	**T4**	**T5**
Time points	**D1 M0**	**D15**	**D31 M1**	**D91 M3**	**D181 M6**	**D195**	**D211 M7**	**D271 M9**	**D361 (ESFU)**
Visit window (days)	**n/a**	**(−3/+3)**	**(−5/+14)**	**(−3/+3)**	**(−5/+14)**	**(−3 /+3)**	**(−5/+14)**	**(−3/+3)**	**(−7/+21)**
Days post-vaccination[2]	**0**	**14 post-vacc 1**	**30 post-vacc 1**	**90 post-vacc 1**	**180 post-vacc 1**	**14 post-vacc 2**	**30 post-vacc 2**	**90 post-vacc 2**	**180 post-vacc 2**
Sampling time points	**pre-vacc**		**post-vacc 1**				**post-vacc 2**		
Recording of medically attended AEs	●	●	●	●	●	●	●	●	●
Recording of SAEs	●	●	●	●	●	●	●	●	●
Recording of AESIs	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[12]	●	●	●	●	●	●	●	●	●
Recording of COVID-19 related AEs and SAEs[13]	●	●	●	●	●	●	●	●	●
Recording of pregnancies	●	●	●	●	●	●	●	●	●
Study Conclusion[14]									●

● study procedure that requires documentation in the individual eCRF.

○ study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents

× study procedure that requires documentation in the study eDiary

The double-line border following D211 indicates the analyses which will be performed on all data (i.e., the data that are as clean as possible) obtained up to D211.

AE = adverse event; AESI = adverse events of special interest; COVID-19 = coronavirus disease 2019; D = day; eCRF = electronic case report form; eDiary = participant diary (electronic diary); ESFU = extended safety follow-up; GSK = GlaxoSmithKline Biologicals; M = month; PC = phone contact; post-vacc = post-vaccination; pre-vacc = pre-vaccination; T = telephone contact; SAE = serious adverse event; V = visit

[1] Home visits are always allowed if deemed suitable and are conducted according to local regulations.

[2] Days post-injection are included to keep track of the intercurrent days between vaccinations, they do not indicate “Study Day”

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

[4] Procedure to be performed prior to any vaccination.
[5] Reminder: appropriate written documentation of the identity of the primary MenACWY vaccination and vaccination date to be provided prior to enrollment. Individuals for whom written documentation is not available may still be enrolled into the study.
[6] The participants must be observed closely for at least 30 minutes after the administration of the vaccine(s)/product. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.
[7] Insufficient blood volume may lead to test cancellation and jeopardize the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.
[8] For information regarding participant discontinuation and withdrawal from the study refer to Section 7.3.
[9] Physical examination must be performed by a qualified health care professional (refer to Appendix 1, Glossary of Terms) in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log.
[10] Frequency or urine pregnancy tests can be established at the site according to local regulations.
[11] Fever is defined as body temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be oral. In case any other route (other than oral) is used for measurement of body temperature/fever, it needs to be recorded in the participant's eCRF.
[12] Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant/participant's parent(s)/legally acceptable representative(s) signs the consent form and assent form (if applicable) to the end of the study.
[13] Diagnosis of coronavirus disease 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 Appendix 4 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 12). In addition, separate COVID-19 specific eCRF form(s) should be completed.
[14] Participants who terminate the study early are recommended to complete certain study-related procedures.

Table 4 Intervals Between Study Visits

Interval	Length of Interval	Allowed Interval
Visit 1 to Visit 2	30 days	25 to 44 days (−5 to +14 days)
Visit 1 to Visit 3	180 days	175 to 194 days (−5 to +14 days)
Visit 3 to Visit 4	30 days	25 to 44 days (−5 to +14 days)
Visit 3 to Last Telephone Contact (T5)	180 days	173 to 201 days (−7 to +21 days)

T = telephone contact

Table 5 Intervals Between Telephone Contacts

Interval	Length of Interval	Allowed Interval (Range)
Visit 1 to Telephone contact T1	14 days	11 to 17 days (−3 to +3 days)
Visit 1 to Telephone contact T2	90 days	87 to 93 days (−3 to +3 days)
Visit 3 to Telephone contact T3	14 days	11 to 17 days (−3 to +3 days)
Visit 3 to Telephone contact T4	90 days	87 to 93 days (−3 to +3 days)
Visit 3 to Last Telephone contact (T5)	180 days	173 to 201 days (−7 to +21 days)

T = telephone contact

2.0 INTRODUCTION

2.1 Study Rationale

Neisseria meningitidis (*N. meningitidis*) bacteria is a leading cause of invasive meningococcal disease (IMD) worldwide, capable of causing outbreaks and epidemics. The best option for the control of IMD is the use of effective vaccines that would include all 5 of the most common serogroups of *N. meningitidis*.

GlaxoSmithKline Biologicals SA (GSK) is developing a combination vaccine intended to protect against 5 of the most prevalent serogroups of *N. meningitidis* (A, B, C, W, and 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. The investigational meningococcal ABCWY (MenABCWY) combination vaccine is based upon 2 established GSK vaccines, the quadrivalent meningococcal ACWY (MenACWY) conjugate vaccine (*Menveo*) and the multi-component recombinant meningococcal B (MenB) vaccine (*Bexsero*), for which significant nonclinical and clinical data have been generated and used to support marketing authorizations in several jurisdictions.

Guidelines regarding meningococcal vaccination in different countries with overall low disease rates vary, but most countries recommend vaccination for defined “at risk” groups based on age, underlying host factors, and anticipated occupational and/or travel-related exposures. In countries (such as Australia, Canada, the United Kingdom, and the United States), a booster dose of conjugate quadrivalent ACWY vaccine is recommended every 5 years for persons at continued high risk (Crum-Cianflone and Sullivan, 2016). For example, the US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent conjugated meningococcal vaccine for adolescents at 11 to 12 years of age with a booster dose at 16 years of age, based on a substantial amount of data showing a robust immune response to a booster dose of MenACWY vaccines in this age group. The ACIP also recommends MenB vaccination in individuals aged 10 years and older who are at increased risk for MenB disease and in adolescents and young adults aged 16 to 23 years regardless of an increased risk for MenB disease.

Based on the current ACIP recommendations for a MenACWY booster dose at 16 years of age and for MenB vaccination at 16 to 23 years of age, there is a need to evaluate the response to MenABCWY vaccine in MenACWY vaccine-primed individuals. In the context of the MenABCWY investigational vaccine development, the MenACWY booster response was evaluated in 2 phase II clinical studies (Sáez-Llorens, 2018; Szenborn, 2018). Although the sample size of these studies was small, a robust anamnestic immune response against MenA, MenC, MenW, and MenY serogroups was demonstrated at 1 month after the administration of

the first dose of the MenABCWY vaccine in participants previously primed with the GSK MenACWY vaccine.

The main purpose of this phase IIIB clinical study is to assess the immunogenicity and safety of the MenABCWY vaccine when administered as a booster in healthy adolescents and young adults, previously primed with a MenACWY vaccine.

2.2 Background

N. meningitidis infections causing 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.

Invasive meningococcal disease occurs when, following an average incubation period of 4 days (range 2 to 10 days), the normally asymptomatically carried encapsulated gram-negative bacterium *N. meningitidis* enters the bloodstream and multiplies. If the bacteria cross the blood-brain barrier, meningitis occurs. Sepsis and meningitis caused by *N. meningitidis* are serious diseases that can be fatal or leave permanent sequelae. In European Union (EU)/European Economic Area countries, despite the availability of advanced medical treatment and effective antibiotics, case-fatality rates are high at approximately 7% to 15%, with most cases caused by serogroup B (ECDC, 2016). Up to one-fifth of survivors suffer long-term sequelae, including mental retardation, hearing loss, and loss of limb use (Rosenstein, 2001). In the US, the overall case-fatality ratio remains at 10% to 15%, and 11% to 19% of survivors have long-term sequelae (Cohn, 2013). Rates of disease are highest in children younger than 1 year of age, followed by a second peak in adolescence (Cohn, 2015).

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 is 0.1 cases per 100 000 population (CDC, 2018).

GSK' MenACWY vaccine is a meningococcal oligosaccharide conjugate vaccine licensed for active immunization to prevent IMD caused by *N. meningitidis* serogroups A, C, W-135, and Y. It is approved for adolescents and adults 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.

A single booster dose of GSK' MenACWY vaccine (*Menveo*) has recently been approved by the US Federal Food and Drug Administration (FDA) for a boosting administration to individuals who are at continued risk for IMD if at least 4 years have elapsed since a prior dose of a meningococcal (serogroups A, C, W-135, Y) conjugate vaccine.

GSK Biologicals' MenB vaccine (*Bexsero*) is approved for use in the EU, US, and several other countries for active immunization to prevent IMD caused by *N. meningitidis* serogroup B. In the EU, the vaccine is indicated for use in individuals 2 months of age and older; in the US, in individuals 10 to 25 years of age. Worldwide, MenB vaccine is approved for use with different schedules depending on the country's jurisdiction; dosage can vary between 2 to 4 doses per participant.

The investigational MenABCWY combination vaccine is based upon the 2 aforementioned well-established GSK's vaccines, MenACWY and MenB. Both vaccines have been extensively tested in clinical trials in order to support marketing authorizations in several jurisdictions.

Refer to the current Investigator's Brochure (IB) for information regarding pre-clinical and clinical studies and epidemiological information of MenABCWY.

2.3 Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of MenABCWY can be found in the IB. Refer to the Product Information (PI) for information regarding the summary of potential risks and benefits of *Bexsero* and *Menveo*.

Benefit considerations include:

- Medical evaluations/assessments associated with this study (e.g., physical examinations).
- Contributing to the process of developing new therapies.
- Potential benefit of receiving the licensed *Bexsero* and *Menveo* vaccines to help protect against meningococcal IMDs caused by *N. meningitidis* serogroups A, B, C, W, and Y.

No significant safety signals have been identified for MenABCWY. Cumulative safety data have not identified new important safety risks. The balance of anticipated benefits and apparent risks associated with MenABCWY continues to be acceptable following the ongoing systematic review of safety data.

Taking into account the measures taken to minimize risk to participants in this study, the potential for risks identified in association with MenABCWY, *Bexsero,* and *Menveo* are justified by the potential benefits that may be afforded to participants.

3.0 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are presented in Table 6.

Table 6 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 1) To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the second MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	• The percentages of participants with a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the second vaccination for the ABCWY group (Day 211, Month 7), and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 2) To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the first MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	• The percentages of participants with a 4-fold rise[1] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the first vaccination for the ABCWY group (Day 31, Month 1), and 1 month after the single dose of MenACWY vaccination for the ACWY group (Day 31, Month 1), relative to baseline (Day 1, Month 0).
Safety To evaluate the safety and reactogenicity of the MenABCWY and MenACWY vaccines.	• The frequencies and percentages of participants with solicited administration site events (i.e., injection site pain, erythema, swelling, induration) and solicited systemic events (i.e., fever [body temperature ≥38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) during the 7 days (including the day of vaccination) following vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group). • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of

Objectives	Endpoints
	vaccination) following vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group). • The percentages of participants with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period (Month 0 to Month 12).
Secondary	
To assess the immune response to MenABCWY (0,6-month schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W, and Y, at pre-vaccination and 1 month after the first and last MenABCWY vaccinations and 1 month after the MenACWY vaccination.	• The percentages of participants with hSBA titers ≥Lower Limit of Quantitation (LLOQ) 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, and – at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1). • The geometric mean titers (GMTs) 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 (Day 211, Month 7) vaccinations for the ABCWY group, and – at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1). • The geometric mean ratios (GMRs) against serogroups A, C, W, and Y: – at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group as compared to baseline (Day 1, Month 0) and – at 1 month after the MenACWY vaccination (Day 31, Month 1) for the ACWY group as compared to baseline (Day 1, Month 0).

Objectives	Endpoints
To assess the immune response to the MenABCWY vaccine (0,6-month schedule) against *N. meningitidis* serogroup B indicator strains, at pre-vaccination and at 1 month after the last MenABCWY vaccination.	• The percentages of participants with hSBA titers ≥LLOQ for each and all serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the last vaccination (Day 211, Month 7) for the ABCWY group. • The percentages of participants with 4-fold rise[1] in hSBA titers against each *N. meningitidis* serogroup B indicator strains at 1 month after the last vaccination (Day 211, Month 7) relative to baseline (Day 1, Month 0) for the ABCWY group. • GMTs against each serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the last vaccination (Day 211, Month 7) for the ABCWY group. • GMRs against each serogroup B indicator strains at 1 month after the last vaccination (Day 211, Month 7) as compared to the baseline (Day 1, Month 0) for the ABCWY group.

CCI [redacted]

Objectives	Endpoints
CCI [redacted]	

AESI = adverse event of special interest; CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentration; GMT = geometric mean titer; GMR = geometric mean ratio; hSBA = human serum bactericidal assay; LLOQ = lower limit of quantitation; *N. meningitidis* = *Neisseria meningitidis*; SAE = serious adverse event

[1] Refer to Section 9.0 for the (seroresponse) definition of the 4-fold rise.

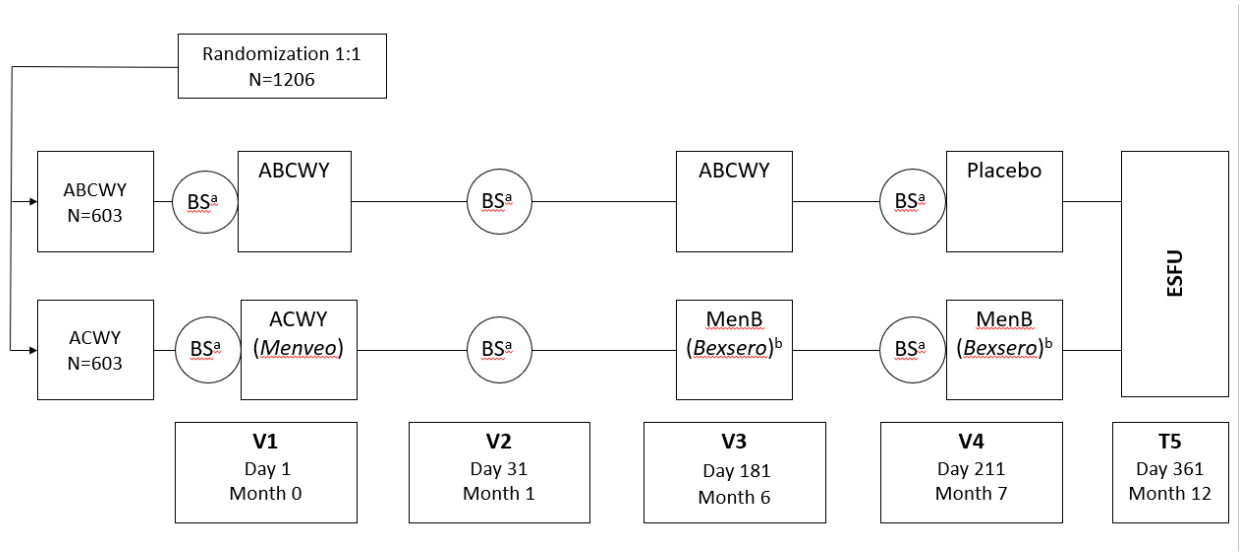
CCI [redacted]

4.0 STUDY DESIGN

4.1 Overall Design

The study design diagram is provided in Figure 1.

Figure 1 Study Design Overview



ACWY = *Menveo*; BS = blood sample; ESFU = extended safety follow-up; MenB = *Bexsero*; N = number of participants; T = telephone contact; V = visit

[a] Insufficient blood volume may lead to test cancellation and jeopardize the statistical power. Hence, every effort must be made to collect blood volume as per protocol requirements.

[b] *Bexsero* is given for compliance with standard of care.

Protocol waivers or exemptions are not allowed except for immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 1.3), are essential and required for study conduct.

- **Type of study:** Self-contained.
- **Experimental design:** Phase IIIB, randomized, controlled, observer-blind, multi-centric, study with 2 parallel study groups.
- **Duration of the study:** The total duration of the study, per participant, will be approximately 12 months (4 visits), including the 6 months of Extended Safety Follow-Up (ESFU) period after the last dose of investigational vaccine (Visit 3, Day 181).
- **Primary completion date (PCD):** Last Participant Last Visit (LSLV) (Day 361).
- **Blinding:** Observer-blind. Refer to Section 6.3.5 for details.
- **Data collection:** Standardized electronic Case Report Form (eCRF). Solicited events will be collected using a Participant Diary (electronic diary [eDiary]).

- **Safety monitoring:** Regular safety follow-up will be done through telephone calls. Safety follow-up calls are calls made to the participant by a qualified study center staff designated by the investigator on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. There will also be ESFU phone call 6 months after the last dose of investigational vaccine (Visit 3, Day 181). This ESFU phone call will also mark the study conclusion. Refer to the Schedule of Events (SoA) (Table 3) and Section 8.3 for details on the safety follow-up.
- **End of study:** Refer to Section 4.4.
- **Study groups:**
  - **ABCWY:** 603 participants will receive 2 doses of the MenABCWY vaccine at Visit 1 (Day 1) and Visit 3 (Day 181) (0,6-month schedule) and 1 dose of placebo at Visit 4 (Day 211).
  - **ACWY:** 603 participants will receive 1 dose of MenACWY vaccine at Visit 1 (Day 1) (single dose) and 2 doses of MenB vaccine at Visit 3 (Day 181) and Visit 4 (Day 211).

Study groups, intervention and blinding foreseen in the study are presented in Figure 1 and Table 7.

See Appendix 1, Glossary of Terms, for definitions of a self-contained study, PCD, solicited events, intervention, blinding, and a qualified health care professional.

Table 7 Study Groups, Intervention, and Blinding Foreseen in the Study

Study Group	Number of Participants	Age (Min to Max)	Intervention	Blinding
ABCWY	603	15 to 25 years (25 years + 364 days)	MenABCWY Placebo	V1 to T5: Observer-blind
ACWY	603	15 to 25 years (25 years + 364 days)	MenACWY MenB	V1 to T5: Observer-blind

MenACWY = *Menveo*; MenB = *Bexsero*; T = telephone contact; V = visit

4.2 Scientific Rationale for Study Design

The study is designed as a randomized, controlled, observer-blind study with 2 parallel groups. This study will evaluate the immunogenicity and safety of the MenABCWY vaccine when administered as a booster in healthy adolescents and young adults, 15 through 25 years of age, previously primed with a MenACWY vaccine. The currently licensed *Menveo* (MenACWY) vaccine will be used as comparator.

In order to let the participants in the ACWY group receive 2 doses of MenB vaccine in line with ACIP recommendations, the participants in this group will receive vaccinations of MenB on Visit 3 (Day 181) and Visit 4 (Day 211). There are no study objectives related to the MenB vaccine, as it will be administered only to ensure standard of care. However, to maintain the study blinding, solicited events (see Appendix 1, Glossary of Terms, for a definition of solicited events) during the 7 days (including the day of vaccination) after the first MenB vaccination will be collected and recorded through eDiary, and unsolicited AEs during the 30 days (including the day of vaccination) during interview with the participant/participant's parent(s)/legally acceptable representative(s) (LAR[s]) at the next visit (refer to the SoA [Table 3] and Section 8.3.6.1 for time and frequency on collection of AEs). Although not part of the study objectives, solicited events and unsolicited AEs after the first MenB vaccination will be reported in the clinical study report (CSR).

For this study, a placebo (saline solution) will be administered in the ABCWY group at Visit 4 (Day 211) (Figure 1). A placebo is the best available option to minimize the potential for reporting bias in collecting information about AEs and to ensure the same number of vaccinations are administered to participants assigned to either of the 2 study groups.

Blood will be taken from all participants at specified time points (Visit 1, Visit 2, and Visit 4 [Figure 1]) (refer to Section 8.1 for details on immunogenicity assessments). Insufficient blood volume may lead to test cancellation and jeopardize the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.

Blood samples will be taken from all participants irrespective of the testing status in order to maintain the study blind. Refer to Section 8.1.1 for further details.

Given the aim of the study is to evaluate the MenABCWY booster response in healthy participants previously primed with MenACWY vaccine, eligible participants must have received a previous vaccination with a quadrivalent meningococcal conjugate vaccine (MenACWY; *Menveo* or *Menactra*) at least 4 years prior to study start.

4.3 Justification for Dose

A number of different vaccine formulations with different amounts of the MenB component of the vaccine were evaluated in MenABCWY phase I and II clinical studies. The MenABCWY formulation that included the same active ingredient composition for outer membrane vesicles (OMV) as *Bexsero*, induced a higher immune response against serogroup B test strains with a comparable reactogenicity profile and no identified safety concerns. Therefore, the formulation with the same active ingredient composition as the MenB (*Bexsero*) and MenACWY (*Menveo*) vaccines was chosen as the final formulation of the MenABCWY investigational vaccine. The dosing schedule for MenB and MenACWY is based on approved schedules for those vaccines while it is not in major contradiction with vaccination schedules in other countries. The

0,6-month schedule for MenABCWY is based on the results of the completed phase II Study V102_15.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she returns or is available for the last scheduled contact as described in the protocol.

End of study (EoS): LSLV (Day 361) or last testing results released for the samples collected at Visit 4 (Day 211)*.

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

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Adherence to the criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardise the scientific integrity or regulatory acceptability of the study or participant safety.

All participants must satisfy ALL of the following criteria at study entry:

1. Participants and/or participants' parents/LARs, who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the eDiary, return for follow-up visits).
2. Written or witnessed/thumb printed informed consent obtained from the participant/participant's parent(s)/LAR(s) of the participant prior to performance of any study specific procedure.
3. Written or witnessed/thumb printed informed assent obtained from participants below the legal age of consent prior to performance of any study specific procedure.
4. Previous vaccination with 1 dose of MenACWY vaccine at an age of 10 years or older, with an interval of at least 4 years between the previous MenACWY vaccine and enrollment (informed consent and assent [as applicable]) into this study.
5. A male or female between, and including, 15 and 25 years of age (i.e., 25 years + 364 days) at the time of the first vaccination.
6. Healthy participants as established by medical history, physical examination, and clinical judgment of the investigator before entering into the study.
7. Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy, or post-menopause.
8. Female participants of childbearing potential may be enrolled in the study, if the participant:

   – has practiced adequate contraception for 30 days prior to vaccination, and
   – has a negative pregnancy test* on the day of vaccination, and
   – has agreed to continue adequate contraception during the entire intervention period and for 30 days after completion of the vaccination series.

   **Note: Urine samples for pregnancy testing will be collected from female participants of childbearing potential at Visit 1, Visit 3, and Visit 4 prior to the vaccination. Frequency or urine pregnancy tests can be established at the site according to local regulations.*

Refer to Appendix 5 for definitions of woman of childbearing potential and adequate contraception.

Refer to Appendix 1, Glossary of Terms, for definitions of the investigator, eligible participants, enrolled participants, and witness.

5.2 Exclusion Criteria

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardize the scientific integrity or regulatory acceptability of the study or safety of the participant.

The following criteria should be checked at the time of study entry. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies.

5.2.1 Medical Conditions

1. Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
2. Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection within 60 days of enrollment.
3. History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s)/product.
4. 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.
5. Progressive, unstable or uncontrolled clinical conditions
6. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
7. 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 (oral/intravenous/intramuscular) for more than 14 consecutive days within 90 days prior to study vaccination until the following post-vaccination blood sample. This will mean prednisone equivalent ≥20 mg/day for adult participants / and ≥0.5 mg/kg/day with maximum ≥20 mg/day for pediatric participants. 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).

8. 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, generalized tonic-clonic seizures, partial complex seizures, partial simple seizures). History of febrile convulsions should not lead to exclusion.
9. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

5.2.2 Prior/Concomitant Therapy

10. Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study vaccine(s)/product during the period beginning 30 days before the first dose of study vaccine(s)/product (Day −29 to Day 1), or planned use during the study period.
11. Previous vaccination against any group B meningococcal vaccine at any time prior to informed consent and assent as applicable (according to the participant's age).
12. Previous vaccination with 2 or more doses of MenACWY vaccine.
13. Administration/planned administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before any dose of study vaccine(s)/product until the following post-vaccination blood sample.
14. Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to any vaccine/product dose until the following post-vaccination blood sample. For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants / and ≥0.5 mg/kg/day with maximum ≥20 mg/day for pediatric participants. Inhaled and topical steroids are allowed.

Refer to the Appendix 1, Glossary of Terms, for a definition of a study vaccine/product.

5.2.3 Prior/Concurrent Clinical Study Experience

15. Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).

Refer to the Appendix 1, Glossary of Terms, for a definition of an investigational vaccine/product.

5.2.4 Other Exclusions

16. Child in care.

17. Pregnant or lactating female.
18. Female planning to become pregnant or planning to discontinue contraceptive precautions (see inclusion criterion #8 for the necessary duration of contraception practice).
19. History of/current chronic alcohol and/or drug abuse.
20. Involvement in the study as a study staff member or being immediate dependents, family, or household member of a study staff member.

Refer to the Appendix 1, Glossary of Terms, for a definition of a child in care.

5.3 Lifestyle Considerations

No dietary, caffeine, alcohol, tobacco use, activity, or other lifestyle restrictions are required.

5.4 Screen Failures

If the individual is determined ineligible for study participation or has not entered into the study for other reasons following informed consent but before randomization, he/she is considered a screen failure.

6.0 STUDY INTERVENTION

A “study intervention” is defined as a set of investigational or marketed product or placebo intended to be administered to a participant during the study.

Refer to the study reference manual for additional details.

6.1 Study Interventions Administered

The study interventions that will be administered in the study are provided in Table 8.

The participants must be observed closely for at least 30 minutes after the administration of the vaccine(s)/product. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.

Table 8 Study Interventions Administered

Study Intervention Name	**MenABCWY**[1,2]		***Menveo***[3,2,4]		***Bexsero***[5]	**Placebo**[5,6]
Vaccine(s)/ Product	MenACWY lyo	rMenB+OMV NZ	MenA	MenCWY	rMenB+OMV NZ	NaCl
Presentation	Vial	Syringe	Vial	Vial	Syringe	Syringe
Dose form	Powder for suspension for injection	Suspension for injection	Powder for solution for injection	Solution for solution for injection	Suspension for injection	Solution for injection
Vaccines(s)/ Product Formulation[7]	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 aluminum hydroxide; Recombinant *N. meningitidis* serogroup B NadA protein (50 µg) adsorbed on aluminum hydroxide; Recombinant *N. meningitidis* serogroup B fHbp fusion protein (50 µg) adsorbed on aluminum hydroxide; Outer membrane vesicles from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed	Meningococcal group A oligosaccharides (10 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (16.7-33.3 µg); Potassium dihydrogen phosphate; Sucrose	Meningococcal group C oligosaccharides (5 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (7.1-12.5 µg); Meningococcal group W-135 oligosaccharides (5 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (3.3-8.3 µg); Meningococcal group W-135 oligosaccharides (5 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (5.6-10 µg); NaCl;	Recombinant *N. meningitidis* serogroup B NHBA fusion protein (50 µg) adsorbed on aluminum hydroxide; Recombinant *N. meningitidis* serogroup B NadA protein (50 µg) adsorbed on aluminum hydroxide; Recombinant *N. meningitidis* serogroup B fHbp fusion protein (50 µg) adsorbed on aluminum hydroxide; Outer membrane vesicles from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg	Sodium chloride (NaCl) (0.9%); Water for injections

Study Intervention Name	**MenABCWY**[1,2]		***Menveo***[3,2,4]		***Bexsero***[5]	**Placebo**[5,6]
		on aluminum hydroxide; Aluminum hydroxide (0.5 mg Al^{3+}); Sucrose; Histidine; NaCl; Water for injections q.s. 0.5 mL[10]		Sodium dihydrogen phosphate monohydrate; Disodium phosphate dihydrate; Water for injections q.s. 0.5 mL	PorA P1.4) adsorbed on aluminum hydroxide; Aluminum hydroxide (0.5 mg Al^{3+}); Sucrose; Histidine; NaCl; Water for injections q.s. 0.5 mL	
Product type	Combination		Biological		Combination	Combination
Type	Study		Control		Additional	Additional
Route of Administration	Intramuscular use		Intramuscular use		Intramuscular use	Intramuscular use
Administration site:						
Location[8]	Deltoid		Deltoid		Deltoid	Deltoid
Laterality[8]	Non-dominant		Non-dominant		Non-dominant	Non-dominant
Number of doses to be administered	2		1		2	1
Volume to be administered[9]	0.5 mL		0.5 mL		0.5 mL	0.65 mL[11]
Packaging, labelling	Refer to study reference manual for details		Refer to study reference manual for details		Refer to study reference manual for details	Refer to study reference manual for details
Manufacturer	GSK Biologicals SA		GSK Biologicals SA		GSK Biologicals SA	GSK Biologicals SA

CRM = cross reacting material; fHbp = factor H binding protein; GSK = GlaxoSmithKline; NaCl = sodium chloride; NHBA = Neisseria heparin binding antigen; NZ = New Zealand

[1] MenABCWY formulation consisting of a MenACWY lyo (lyophilized component) and of a rMenB+OMV liquid component, to be reconstituted together before administration (0.5 mL) by qualified health care practitioner (refer to Appendix 1, Glossary of Terms).

[2] Investigational vaccine.

[3] *Menveo* commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component, to be reconstituted together before administration (0.5 mL) by qualified health care practitioner (refer to Appendix 1, Glossary of Terms).

[4] In the US, the approved specifications for *Menveo* are described as MenA lyo: MenA=10µg, CRM197=12.5 µg-33 µg; Potassium dihydrogen phosphate; sucrose and MenCWY liquid: MenC=5µg; CRM197=6.25 µg-12.5 µg; MenW=5 µg,CRM197=3.3 µg-10 µg; MenY=5µg,CRM197=3.3 µg-10 µg; Sodium chloride; Sodium dihydrogen phosphate monohydrate; Disodium phosphate dihydrate; water for injections q.s. 0.5 mL.

[5] Non-investigational vaccine or placebo.

[6] Administered in the ABCWY group at Visit 4 to maintain the study observer-blind.

[7] The composition per dose is presented here.

[8] 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.

[9] Refer to the study reference manual for details.

[10] 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 present in commercial *Bexsero* to 0.640 g in the MenB component, used to reconstitute MenABCWY. Refer to the study reference manual for details.

[11] The volume of the saline PFS may be between 0.6 mL and 0.8 mL. The full volume is to be injected.

6.2 Preparation/Handling/Storage/Accountability

The study vaccine(s)/product must be stored in a safe, locked place at the temperature specified on the vaccine/product label. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded.

Only authorized study personnel should be allowed access to the study vaccine(s)/product. Storage conditions will be assessed by the sponsor's designee (IQVIA, see the study administrative structure in Table 16) during pre-study activities. Refer to the study reference manual for more details on storage and handling of the study vaccine(s)/product.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for the study vaccine(s)/product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study vaccine(s)/product using the Product Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Identification

Participant identification numbers (IDs) will be assigned sequentially to the participants who have consented or provided assent with consent from each participant's parent(s)/LAR(s) to participate in the study, according to the range of Participant IDs allocated to each study center. The Participant IDs will be documented in the Screening and Enrollment log.

The eligibility of the participant will be determined based on the inclusion and exclusion criteria listed in Section 5.0. The Participant ID will be the participant's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study. If the participant is terminated from the study, his/her Participant ID cannot be re-assigned.

6.3.2 Randomization to Study Intervention

All eligible participants will be centrally randomized using Interactive Voice Response System (IVRS) randomization (refer to Appendix 1, Glossary of Terms, for a definition of IVRS). Before the study is initiated, login information and directions for the IVRS will be provided to each study center.

The participants will receive a unique treatment number (refer to Appendix 1, Glossary of Terms, for a definition of a treatment number). Once a treatment number has been assigned, it cannot be re-assigned. To allow the sponsor to take advantage of greater rates of recruitment in this multicenter study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

6.3.3 Intervention Allocation to the Participant

The target sample size to be enrolled in this study is 1206 participants to be assigned to the 2 study groups in a 1:1 ratio:

- **ABCWY:** 603 participants will receive 2 doses of the MenABCWY vaccine at Visit 1 (Day 1) and Visit 3 (Day 181) (0,6-month schedule) and 1 dose of placebo at Visit 4 (Day 211).
- **ACWY:** 603 participants will receive 1 dose of MenACWY vaccine at Visit 1 (Day 1) (single dose) and 2 doses of MenB vaccine at Visit 3 (Day 181) and Visit 4 (Day 211).

Refer to Section 9.2 for a detailed description of the criteria used in the estimation of sample size.

The system's randomization algorithm will use a minimization procedure accounting for country. Upon providing the Participant ID, the randomization system will determine the study group and will provide the treatment number to be used for the first vaccination. The treatment number(s) to be used for subsequent dose administration(s) will be provided by the same randomization system.

See Appendix 1, Glossary of Terms, for a definition of a treatment number.

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

When the specified randomization system is not available, refer to the randomization system user guide or the study reference manual for specific instructions.

Refer to the study reference manual for additional information relative to the treatment number allocation.

6.3.4 Allocation of Participants to Assay Subsets

Immunogenicity assessments are planned as outlined in Section 8.1.

Refer to Section 9.3 for descriptions of analysis populations.

6.3.5 Blinding and Unblinding

6.3.5.1 Blinding

Data will be collected in an observer-blind manner, i.e., participants, investigators, and teams responsible for assessment of any study endpoints will be blinded to the administered vaccine(s)/product. Study vaccine(s)/product will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review, or the entry of any study endpoint (i.e., reactogenicity, safety, immunogenicity).

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

6.3.5.2 Emergency Unblinding

Unblinding a participant's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the participant.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention through IVRS. At study activation, the study centers will be provided instructions and/or other applicable information for emergency unblinding.

The Interactive Response Technology used by the IVRS provider will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Medical Monitor (see the definition in Appendix 1, Glossary of Terms) prior to unblinding unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, the IQVIA's Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. A participant may continue in the study if that participant's intervention assignment is unblinded.

In the event of a Quality Assurance audit, the auditor(s) may be allowed access to unblinded study treatment information records to verify that randomization/study vaccine(s)/products dispensing has been done accurately.

A non-investigator physician (e.g., physician from emergency room) or participant/caregiver (see Appendix 1, Glossary of Terms, for a definition of a

caregiver)/family member may also request emergency unblinding. Instructions for this will be provided to the participant/participant's parent(s)/LAR(s) at enrollment.

6.4 Study Intervention Compliance

When participants are dosed at the study center, they will receive study intervention from the authorized qualified study center staff listed on the site log. This study center staff member will prepare and administer the vaccine(s)/product and will be unblinded to the intervention but will not participate in any post-injection participant assessments. A blinded observer will participate in the participant's post-injection assessments, perform clinical evaluations and record the clinical data. A delegated second-shift or back-up study staff member can be assigned to perform any of these activities. Only blinded staff can participate in any clinical evaluations and recording of clinical data. The date of each dose administered at the study center will be recorded in the source documents and in the eCRF. The dose of study intervention and Participant ID will be confirmed at the time of dosing by a study staff member other than the person administering the study intervention.

Refer to the SoA (Table 3) for the study intervals.

6.5 Concomitant Therapy

At each study visit/contact, the investigator or authorized study center staff member should question the participant and/or the participant's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the participant.

The following concomitant medications/products/vaccines must be recorded in the eCRF:

- Any concomitant medications/products/vaccines administered for the prevention or treatment of a solicited event or AE to be recorded as per the protocol-specified reporting period (see Section 8.3.6.1).
- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the participant from the study (refer to the Section 5.2.2 for further details).
- Any concomitant medications/products/vaccines relevant to a serious adverse event (SAE) or an AE of special interest (AESI) (see definitions in Appendix 4) to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/AESI. Concomitant medications relevant to SAEs and AESI must be recorded on the Expedited AE Report.
- Any concomitant vaccination administered in the period starting 14 days before the first dose of study vaccine(s) and ending at the last study contact (Day −14 to Day 361).
- 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 antipyretic 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 is oral.

- 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 blood sample withdrawal (see Section 6.7 for criteria for temporary delay of vaccination).

Any concomitant medications or products taken during the study 14 days before the first dose of study vaccine(s) and ending at the last study contact that don't fall under the listed conditions, should also be recorded if deemed important per investigator's judgment.

The reason for use, dates of administration (start and end dates) and dosage information (dose and frequency) for medications/products/vaccines will be recorded in the eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6 Dose Modification

Not applicable.

6.7 Criteria for Temporary Delay for Enrollment and/or Vaccination and/or Blood Sampling

Enrollment and/or vaccination and/or blood sampling may be postponed within the permitted time interval until transient circumstances cited below are resolved:

- Acute disease and/or fever at the time of vaccination. Refer to the SoA (Table 3) for fever definition and preferred location for measuring temperature in this study.
- Significant acute illness within the previous 7 days.
- Receipt of systemic antibiotics within 3 days prior to blood sampling visit (Visit 1, Visit 2, and Visit 4) (this will defer the blood draw).
- Receipt of a vaccine not foreseen by the study protocol administered during the period starting 7 days (for inactivated vaccine) or 14 days (for live vaccines) days

before each dose and ending 7 days (for inactivated vaccine) or 14 days (for live vaccines) after each dose of vaccine(s)/product administration*.

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

Under such circumstances, a participant may be considered eligible for study enrollment and/or vaccination after the appropriate window for delay described above, or as defined by local health authorities, has passed and inclusion/exclusion criteria have been re-checked, and if the participant is confirmed to be eligible.

6.8 Contraindications to Subsequent Vaccine(s) Administration

Participants must be evaluated to confirm they are eligible for subsequent vaccination before administering each additional study vaccine dose.

Participants who meet any of the criteria listed below or criteria listed in Section 5.2 should not receive additional vaccinations. However, these participants should be encouraged to continue other study procedures at the discretion of the investigator (refer to Appendix 4 for instructions on follow-up of AEs). The relevant criteria for discontinuing vaccination must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant 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 participant to unacceptable risk from subsequent vaccination. Refer to Appendix 1, Glossary of Terms, for the definition of AESIs.
- Occurrence of a new potential immune-mediated diseases (pIMD) or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgment prior to administering the next dose of the vaccine(s)/product. Refer to Appendix 1, Glossary of Terms, for the definition of pIMDs.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Anaphylaxis following the administration of vaccines.

- Pregnancy.
- 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.

6.9 Intervention After the End of the Study

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

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

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

Refer to Section 8.1.5 for information regarding the immunological correlates of protection.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Reasons for Discontinuation/Withdrawal

- The participant may withdraw or participant's parent(s)/LAR(s) may withdraw a participant from the study at any time on request, or a participant may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.
- If the participant/participant's parent(s)/LAR(s) withdraw consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant is withdrawn from the study, the participant/participant's parent(s)/LAR(s) may request destruction of any samples taken and not tested, and the investigator must document this in the study center study records.

Participants who discontinue study intervention or are withdrawn from the study will not be replaced. The eCRF should be completed as much as possible.

If a participant is withdrawn from the study because he/she/the participant's parent(s)/LAR(s) have withdrawn consent and provided the reason for its withdrawal, the investigator must document this reason in the eCRF.

7.2 Discontinuation of Study Intervention

"Discontinuation" of study intervention (study vaccine(s)/product) means any participant who has not received all planned doses of vaccine(s)/product. A participant who discontinued study vaccine(s)/product may, if deemed appropriate by the investigator, continue other study procedures (e.g., safety or immunogenicity) if planned in the study protocol.

The primary reason for premature discontinuation of the study vaccine(s)/product will be documented on the eCRF based on the following:

- AE requiring expedited reporting to IQVIA
- Unsolicited non-serious AE
- Solicited AE
- Protocol deviation
- Not willing to be vaccinated
- Other (specify)

7.3 Participant Discontinuation/Withdrawal from the Study

A participant 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 participant from the date of withdrawal/last contact.

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

Investigators or designated study center personnel will attempt to contact those participants who do not return for scheduled visits or follow-up.

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

The primary reason for study withdrawal will be documented in the eCRF based on the list below:

- AEs requiring expedited reporting to IQVIA
- Unsolicited non-serious AE
- Solicited AE
- Protocol deviation
- Withdrawal by participant, not due to an AE (see Section 7.1)
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn from the study as result of an SAE/AE until the event is resolved (refer to Appendix 4 for instructions on follow-up of AEs).

7.4 Lost to Follow-up

A participant will be considered "lost to follow-up" if he/she fails to return for scheduled visits and is unable to be contacted by the study center.

Refer to the study reference manual for a description of the actions to be taken before considering the participant as lost to follow-up.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 3).
- Adherence to the protocol is required for study conduct.
- Protocol waivers or exemptions are not allowed unless necessary for the management of an immediate safety concerns.
- The investigator is not allowed to do testing on samples outside of what has been agreed upon by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).
- Immediate safety concerns should be discussed with IQVIA as soon as they occur or when the study team is aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.
- All screening evaluations (i.e., eligibility criteria check) must be completed and the results reviewed before confirming that potential participants meet all eligibility criteria.
- The investigator will maintain a screening log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.
- The study reference manual provides the investigator and study center personnel with administrative and detailed technical information that does not impact participant safety.

8.1 Immunogenicity Assessments

Collected biological 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.

Future findings may make it desirable to use the samples acquired in this study for future research not described in this protocol. Therefore, all participants in countries where this is allowed will be asked to give a specific consent to allow the sponsor or a contracted partner to use the samples for future research. Future research will be participant to IEC/IRB approval if required per local legislation.

Additional serological assays may be performed in the future to further characterize the disease and/or the antibody response to the antigens included in the study vaccines or hSBA against an additional panel of strains of *Neisseria* species. These assays may not be represented in the objectives/endpoints of the study protocol.

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

Sample testing will be done in accordance with the recorded consent of the individual participant/participant's parent(s)/LAR(s).

If additional testing is performed, the marker priority ranking given in the Section 8.1.3 may be changed.

Collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performed the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with participant consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK.

8.1.1 Biological Samples

An overall volume of approximately 60 mL of blood per participant will be collected during the entire study period.

Refer to Table 9 and the SoA (Table 3) for details of blood volumes collected for different assessments.

Table 9 Biological Samples

Sample Type	Quantity	Time Point	Subset Name[1]
Blood	Approximately 20 mL[2]	Visit 1 (Day 1)	Not applicable
Blood	Approximately 20 mL[2]	Visit 2 (Day 31)	Not applicable
Blood	Approximately 20 mL[2]	Visit 4 (Day 211)	Not applicable

[1] Refer to Section 6.3.4 and Section 8.1 for information regarding assay subsets.

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

8.1.2 Laboratory Assays

All laboratory testing will be performed at GSK's laboratory or in a laboratory designated by GSK.

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

Immunogenicity of the vaccine against serogroups A, B, C, W, and Y will be evaluated with the serum bactericidal assay using exogenous source of human complement (hSBA). The 4 indicator strains representing serogroups Men A, C, W, and Y will be tested in the hSBA using the agar-overlay technology, while the 4 indicator strains representing serogroup MenB will be tested in the hSBA using the manual (tilt) technology.

The induction of anti-polysaccharide antibodies directed against serogroup A, C, W, and Y meningococci following MenACWY vaccination may be measured by Enzyme-Linked Immunosorbent Assay (ELISA). The ELISA procedure is used to detect the amount of

serum immunoglobulin G (IgG) antibodies in response to specific *N. meningitidis* polysaccharide antigens. See Table 10 for details.

Table 10 Laboratory Assays

System	Component	Method	Laboratory
Serum	N men A (3125) Ab	hSBA	GSK[1] or laboratory designated by GSK Biologicals
	N men C (C11) Ab		
	N men W (240070) Ab		
	N men Y (860800) Ab		
Serum	N men B fHbp (M14459) Ab	hSBA	
	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[2]	
	N. men C Ab IgG		
	N men W Ab IgG		
	N men Y Ab IgG		

Ab = Antibody; ELISA = enzyme-linked immunosorbent assay; fHbp = factor H binding protein; hSBA = serum bactericidal assay using human complement; IgG = Immunoglobin G; N men = *Neisseria meningitidis*; NadA = Neisserial adhesin A; NHBA = Neisseria Heparin Binding Antigen; PorA = Porin A

[1] GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart or Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Siena, Italy, or to Nexelis in Marburg, Germany, or other external laboratories.

[2] ELISA 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 and submitted prior to the submission of the clinical study report.

Refer to Appendix 3 for a detailed description of the assays performed in the study. The addresses of clinical laboratories used for sample analysis will be provided in a separate document.

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

Laboratory/analyte results that could unblind the study will not be reported to study centers or other blinded personnel until the study has been unblinded.

8.1.3 Immunological Read-outs

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 11. The subsets for immunological read-outs will be randomly selected from the pool of blood draws and will be described in separate randomization list(s) and handed over to the laboratory. The trigger for the randomization list(s) will be completion of blood draws for a given visit.

Table 11 Immunological Read-outs

Blood Sampling Time Point		No. Planned Participants[1]	Method[2]	Component	Components Priority Rank[3]
Type of Contact and Time Point	Sampling Time Point				
Visit 1 (Day 1)	Pre-Vacc 1	1206[4]	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
		209[4]	hSBA	N men B (M14459) Ab	2
			hSBA	N men B (M13520) Ab	2
			hSBA	N men B (96217) Ab	2
			hSBA	N men B (NZ98/254) Ab	2
Visit 2 (Day 31)	Post-Vacc 1	1206[4]	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
		209[4]	hSBA	N men B (M14459) Ab	2
			hSBA	N men B (M13520) Ab	2
			hSBA	N men B (96217) Ab	2
			hSBA	N men B (NZ98/254) Ab	2
Visit 4 (Day 211)	Post-Vacc 2	270[4]	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
		209[4]	hSBA	N men B (M14459) Ab	2
			hSBA	N men B (M13520) Ab	2
			hSBA	N men B (96217) Ab	2
			hSBA	N men B (NZ98/254) Ab	2

Ab = antibody; hSBA = serum bactericidal assay using human complement; IgG = Immunoglobin G; N men = *Neisseria meningitidis*; Pre-Vacc = pre-vaccination; Post-Vacc = post-vaccination

[1] Approximate number of participant samples tested.
[2] For details regarding the method refer to Table 10.
[3] Priority ranking for the serum bactericidal assay using human complement (hSBA) testing using the 8 indicator strains may be participant to change during the study (e.g., in case of requalification, revalidation or standardization). This will be documented in a protocol amendment
[4] For the N Men B test strains: samples from 189 participants in the ABCWY group and 20 participants in the control group to maintain the study blinding at all time points (Day 1, Day 31, and Day 211). For the N Men A, C, W, Y serogroups: samples from all study participants will be tested at Day 1 and Day 31, and samples from 250 participants in the ABCWY group and 20 participants in the control group to maintain the study blinding will be tested at Day 211. Evaluation of the tertiary objective is participant to the availability of samples and may or not be performed.

8.1.4 Clinical Safety Laboratory Assessments

A urine pregnancy test will be conducted as needed for women of childbearing potential (refer to Section 8.3.3). The test will be conducted locally according to the clinical laboratory manual and the SoA (Table 3).

8.1.5 Immunological Correlates of Protection

No generally accepted immunological correlate (see Appendix 1, Glossary of Terms, for a definition of immunological correlate) of protection has been demonstrated so far against *N. meningitidis* serogroups A, B, W-135, and Y.

An hSBA titer ≥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.

Refer to Section 6.9 for details regarding treatment for non-responders.

8.2 Collection of Demographic Data and Other Baseline Characteristics

At Visit 1, demographic data such as date of birth (month and year), gender, race, and ethnic origin will be recorded in the participant's eCRF. Height and weight will be measured using calibrated equipment, and the body mass index will be derived.

8.3 Safety Assessments

The investigator and investigator's designee(s) are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and investigator's designee(s) remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study treatment or study.

Data will be collected in an observer-blind manner, i.e., participants, investigators, and teams responsible for assessment of any study endpoints will be blinded to the administered vaccine(s)/product.

Safety follow-up calls are calls made to the participant by a qualified health care professional designated on the Study Site Responsibility Delegation Log. These calls will follow a script which will facilitate the collection of relevant safety information.

8.3.1 Medical History

Participant's vaccination history will be obtained by interviewing the participant/participant's parent(s)/LAR(s) and/or review of the participant's medical records. The appropriate written documentation of the identity of the primary MenACWY vaccination and vaccination date should to be provided prior to enrollment. Individuals for whom written documentation is not available may still be enrolled into the study. Any pre-existing participant conditions, signs and/or symptoms present prior to the first vaccination will be recorded in the eCRF.

Medical history will be collected at Visit 1, including but not limited to any medical history that may be relevant to participant eligibility for study participation such as prior vaccinations, concomitant medications (refer to Section 5.2.2), and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

8.3.2 Physical Examination

At Visit 1, a general physical examination will be performed by a qualified health care professional. "Qualified health care professional" refers to any licensed or certified health care practitioner who is permitted by institutional policy to perform protocol-required procedures and who is identified within the Study Staff Signature Log.

The physical examination may include examination of organ systems that are relevant to the investigation based on medical history and review of systems (e.g., measurement of heart rate, blood pressure, height and weight, body temperature).

Review of systems is a structured interview that queries the participant and/or parent(s)/LAR(s) as to any complaints the participant has experienced across each organ system.

At Visits 2 through 4, a brief symptom-directed physical examination is to be performed if necessary according to symptoms the participant/participant's parent(s)/LAR(s) has either recorded in the eDiary or reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based only on review of the participant's reported AEs and concomitant medication use. This assessment may include measurement of heart rate and temperature. It should be performed prior to the administration of study vaccine(s)/product and should be documented in source documents.

Should the physical assessment reveal any abnormal values or events, these must be documented in the eCRF AE Form.

If the investigator determines that the participant's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the allowed interval between study visits (Table 4) (refer to Section 6.7).

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. Concomitant medications should be documented in the eCRF.

8.3.3 Pregnancy Test

Female participants of childbearing potential must perform a urine pregnancy test prior to any study vaccine administration. Pregnancy testing must be performed even if the participant is menstruating at the time of the study visit. The study vaccine(s)/product may only be administered if the pregnancy test is negative.

Refer to the Appendix 5 for the contraceptive guidance and information on study continuation for a participant who becomes pregnant during the study.

8.3.4 Warnings and Precautions to Vaccination

Warnings and precautions to vaccination must be checked at the beginning of each vaccination visit prior to any study vaccine(s)/product administration.

Please refer to the IB for MenABCWY and to the approved product label/package insert for the commercial *Bexsero* and *Menveo* vaccines.

8.3.5 Pre-vaccination Body Temperature

The body temperature (preferably oral*) of each participant needs to be measured prior to any study vaccines administration. If the participant has fever, defined as body temperature ≥38.0°C/100.4°F regardless the location of measurement, on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (refer to Section 6.7).

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

8.3.6 Adverse Events

8.3.6.1 Time Period and Frequency for Collecting AE and SAE Information

Solicited administration site and systemic events occurring during the 7 days (including the day of vaccination) following vaccination at Day 1 and Day 181, will be collected using a pre-defined participant eDiary (refer to the SoA [Table 3]). See Appendix 1,

Glossary of Terms, for definitions of various types of AEs and to Appendix 4 for further details on solicited AEs. Solicited administration site and systemic events that are ongoing after the 7-day reporting period will continue to be recorded in the eDiary until resolution or up to 30 days post-vaccination (i.e., recording period for unsolicited AEs) whichever occurs first and do not need to be entered as an AE in the AE eCRF or the participant'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 analyzed as unsolicited AEs (i.e., in the Unsolicited Safety Set).

Unsolicited AEs are AEs that are not solicited using a participant eDiary occurring during the 30 days (including the day of vaccination) following vaccination at Day 1 and Day 181 (refer to the SoA [Table 3]), and 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 AEs leading to vaccine/study withdrawal, medically attended AEs, SAEs, pregnancies, and AESIs will begin at Day 1 (i.e., the first receipt of study vaccines) and will end 6 months following administration of the last dose of investigational vaccine for each participant (i.e., study end). Refer to Section 8.3.6.4 for instructions on reporting of SAEs, pregnancies, and AESIs.

In addition to the above-mentioned reporting requirements and in order to fulfill 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 consent until the participant is discharged from the study. Details regarding follow-up of AEs, SAEs, and AESIs are provided in Appendix 4.

An overview of the protocol-required reporting periods for solicited administration site and systemic events, unsolicited AEs, medically attended AEs, AEs leading to vaccine/study withdrawal, SAEs, AESIs, SAEs related to study participation or concurrent GSK medication/vaccine and pregnancy is provided in Table 12.

Table 12 Timeframes for Collecting and Reporting of Safety Information

Time Points	**Pre-Vacc**[1]	**Vacc 1**	**Post-Vacc 1**	**PC**	**Post-Vacc 1**	**PC**		**Vacc 2**	**Post-Vacc 2**	**PC**	**Post-Vacc 2**	**PC**	**PC**
Visit	**-**	**V1**		**T1**	**V2**	**T2**		**V3**		**T3**	**V4**	**T4**	**T5 ESFU**
Day	**-**	**D1**	**D7**[2]	**D15**	**D31**[3]	**D91**		**D181**	**D187**[2]	**D195**	**D211**[3]	**D271**	**D361**
Month	**-**	**M0**	**M0**		**M1**	**M3**		**M6**	**M6**		**M7**	**M9**	**M12**
Solicited administration site and systemic events[4,5]													
All unsolicited AEs[4,6]													
AEs leading to intervention/study withdrawal[4,6]													
Medically attended AEs[4,6]													
SAEs[4,6]													
AESIs[4]													

Time Points	**Pre-Vacc**[1]	**Vacc 1**	**Post-Vacc 1**	**PC**	**Post-Vacc 1**	**PC**		**Vacc 2**	**Post-Vacc 2**	**PC**	**Post-Vacc 2**	**PC**	**PC**
Visit	**-**	**V1**		**T1**	**V2**	**T2**		**V3**		**T3**	**V4**	**T4**	**T5 ESFU**
Day	**-**	**D1**	**D7**[2]	**D15**	**D31**[3]	**D91**		**D181**	**D187**[2]	**D195**	**D211**[3]	**D271**	**D361**
Month	**-**	**M0**	**M0**		**M1**	**M3**		**M6**	**M6**		**M7**	**M9**	**M12**
SAEs related to study participation or concurrent GSK medication/vaccine[4,6]													
Pregnancy													

AEs = adverse events; AESIs = adverse events of special interest; D = day; ESFU = extended safety follow-up; M = month; PC = phone contact; SAE = serious adverse event; T = telephone call; V = visit; Vacc = vaccination.

1 Consent obtained.

2 Seven consecutive days post-vaccination (including the day of vaccination).

3 Thirty consecutive days post-vaccination (including the day of vaccination).

4 All concomitant medications/products, except vitamins and dietary supplements, administered to treat an AE/SAE, occurred during the entire study period (Day 1 to Day 361), should be recorded in the eCRF and participant's medical records.

5 All solicited administration site and systemic events that occur during the 7 days following administration of study vaccine at Visit 1 (Day 1) and Visit 3 (Day 181).

6 For coronavirus disease 2019 (COVID-19) related AEs/SAEs, follow routine AE/SAE collection and reporting processes as outlined in the protocol.

The investigator or investigator's designee will record and immediately report all SAEs to IQVIA via the Expedited AE Reporting Form. This reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Appendix 4. The investigator will submit any updated SAE data to IQVIA 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 periods defined in Table 12. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine(s)/product, the investigator will promptly notify IQVIA.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.6.2 Method of Detecting AEs and SAEs

Methods of detecting and recording AE/SAE/AESI/pregnancies, and the assessment of AE/SAE intensity, causality and outcome are provided in Appendix 4.

Open-ended and non-leading verbal questioning of the participants/participants' parents/LARs is the preferred method of acquiring information related to an AE/SAE/AESI/pregnancy.

8.3.6.3 Follow-up of AEs and SAEs

Instructions on follow-up of AEs and SAEs are provided in Appendix 4.

8.3.6.4 Regulatory Reporting Requirements for SAEs

Once an investigator becomes aware that a study participant has experienced an SAE/AESI/pregnancy, he/she must report it to IQVIA within the timeframes provided in Table 13. This is essential for meeting legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs, the investigator will always provide an assessment of causality at the time of the initial report, as defined in the Appendix 4.

Local regulatory requirements and sponsor's policy for the preparation of an investigator safety report for suspected unexpected serious adverse reactions (SUSARs) must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has a legal responsibility to notify local authorities and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor

will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Refer to Appendix 4 for further details regarding the reporting of SAEs/AESIs/pregnancies.

Table 13 Timeframes for Submitting SAEs, Pregnancies, and AESIs

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAE	24 hours[1,2,3]	electronic Expedited AE Report	24 hours[1]	electronic Expedited AE Report
Pregnancy	24 hours[1]	electronic Pregnancy Report	24 hours	electronic Pregnancy Report
AESI	24 hours[2,4]	electronic Expedited AE Report	24 hours[1]	electronic Expedited AE Report

AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event

[1] Timeframe allowed after receipt or awareness of the information by the investigator/study center staff.

[2] The investigator will be required to confirm review of the SAE/AESI causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the SAE/AESI.

[3] For coronavirus disease 2019 (COVID-19) related SAEs, reports should be submitted following routine procedures for SAEs.

[4] Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.

8.3.6.5 Treatment of Adverse Events

Any medication administered for the treatment of an SAE/AESI should be recorded in the Expedited AE Report of the participant's eCRF screen (refer to Appendix 4).

8.3.6.6 Participant Card

The investigator or investigator's designee must provide the participant/participant's parent(s)/LAR(s) with a "participant card" containing information about the clinical study. The participant/participant's parent(s)/LAR(s) must be instructed to keep the participant card in his/her/their possession at all times throughout the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator.

8.3.7 Treatment of Overdose

8.3.7.1 Vaccine Administration Error

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.

Any vaccine administration error detailed in this protocol must be reported as an AE, and if overdose is associated with an SAE, it must be reported as such within 24 hours to IQVIA.

8.3.7.2 Overdose of Study Vaccine

An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in 1 dose of study vaccine MenABCWY and/or MenB and/or MenACWY.

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

Any overdose of study vaccine detailed in this protocol must be reported as an AE, and if overdose is associated with an SAE, it must be reported as such within 24 hours to the sponsor's designee.

8.3.8 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 Appendix 1 for the definition of a combination product and a medical device deficiency.

8.3.8.1 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 the sponsor's designee. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to the sponsor's designee within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Appendix 4 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 causality of the deficiency. 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 the sponsor's designee within 24 hours.

8.3.8.2 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 in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. Refer to Appendix 4 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.

8.4 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.5 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.6 Genetics

No samples will be collected during this study for genetic or pharmacogenetic research.

8.7 Biomarkers

No biomarkers will be collected for pharmacogenetic research in this study.

8.8 Health Outcomes

No economic health outcome measures will be collected in this study.

8.9 Study Procedures During Special Circumstances

During special circumstances (e.g., coronavirus disease 2019 [COVID-19] pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.

- If an eDiary device was provided to the participant, it may be returned to the study center by conventional mail after the end of the relevant data collection period.
- Visits for suspected AEs may take place in a different location* other than the study center or at participant's home. If this is not feasible, then the medical evaluation of AEs may take place virtually with documentation of symptoms by other means of communication (e.g., phone call or videoconference), if possible.
- Biological samples may be collected at a different location* other than the study center or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

**Note: It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH Good Clinical Practice (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 study center staff other than the designated study center. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 pandemic (version 2, 27 March, 2020) for more details.*

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

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The following study hypotheses are ordered into 2 families that will be tested in a fixed sequential design with full alpha propagation. Family 1 will be tested first and family 2 will only be tested if the hypothesis in family one is successfully demonstrated.

First Co-Primary Immunogenicity Objective (Family 1)

The first co-primary immunogenicity objective is to demonstrate the immunological non-inferiority (NI) of the antibody response to MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with MenACWY, as measured by percentage of participants with 4-fold rise in hSBA titer against each of the *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the second MenABCWY vaccination and 1 month after the MenACWY vaccination (single dose). This translates to the following hypotheses:

H_0: $(p1\_MenABCWY_{(i)} - p1\_MenACWY_{(i)} \leq -10\%$

vs.

H_1: $(p1\_MenABCWY(i) - p1\_MenACWY(i) > -10\%$

Where $p1\_MenABCWY_{(i)}$ denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the second vaccination of MenABCWY group and $p1\_MenACWY_{(i)}$ denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the single vaccination of MenACWY group.

NI criterion: Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the percent difference in the 4-fold rise in hSBA titers (p_MenABCWY– p_MenACWY) is above −10% for each serogroup A, C, W, and Y.

Second Co-Primary Immunogenicity Objective (Family 2)

The second co-primary immunogenicity objective is to demonstrate the immunological NI of the antibody response to MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with MenACWY, as measured by percentage of participants with 4-fold rise in hSBA titer against each of the *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the first MenABCWY vaccination and 1 month after the MenACWY vaccination (single dose). This translates to the following hypotheses:

H_0: $(p2\_MenABCWY_{(i)} - p2\_MenACWY_{(i)} \leq -10\%$

vs.

H_1: (p2_MenABCWY(i) – p2_MenACWY(i) >−10%

Where $p2\_MenABCWY_{(i)}$ denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the first vaccination of MenABCWY group and $p2\_MenACWY_{(i)}$ denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the single vaccination of MenACWY group.

NI criterion: Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the percent difference in the 4-fold rise in hSBA titers (p_MenABCWY–p_MenACWY) is above −10% for each serogroup A, C, W, and Y.

9.2 Sample Size Determination

The sample size calculation was based on data from the MenABCWY, V102_03E1 study after adjusting for the variabilities due to different settings of the study (e.g., differences in population, differences in antibody assays, and different strain for serogroup A) (Table 14).

Assuming that MenACWY group will induce a 4-fold rise in about 95% of the participants for each of the 4 serogroups; MenABCWY will induce a 4-fold rise in about 91% of the participants for A and W serogroups, and 93% of the participants for C and Y serogroups; and using a 1-sided score test (Miettinen, 1985), non-inferiority margin of −10% and actual margins as given in Table 14, an estimated number of evaluable participants (n=542) and individual powers of 96.00%, 99.95%, 96.00%, and 99.95% for each A, C, W, and Y serogroup test, will give a global power of 90% to demonstrate NI of MenABCWY vs MenACWY.

Family 1: Assuming that MenABCWY and MenACWY groups will induce a 4-fold rise in about 95% of the participants for each of the 4 serogroups (Table 14), and using a 1-sided score test (Miettinen, 1985), non-inferiority margin of −10% and actual margin of 0%, an estimated number of evaluable participants (n = 225) and individual powers of 99.87% for each A, C, W, and Y serogroup test, will give a global power of 99.48% to demonstrate non-inferiority of MenABCWY versus MenACWY.

Family 2: Assuming that MenACWY group will induce a 4-fold rise in about 95% of the participants for each of the 4 serogroups; MenABCWY will induce a 4-fold rise in about 91% of the participants for A and W serogroups, and 93% of the participants for C and Y serogroups; and, using a 1-sided score test (Miettinen, 1985), non-inferiority margin of −10% and actual margins as given in Table 14, an estimated evaluable participants (n=542) and individual powers of 96.00%, 99.95%, 96.00%, and 99.95% for each A, C, W, and Y serogroup test, will give a global power of 91% to demonstrate NI of MenABCWY versus MenACWY.

For the multiplicity adjustment, all hypotheses will be ranked into two families according to the following power of test:

Table 14 Power to Demonstrate Immunological Non-inferiority for Serogroups A, C, W, and Y of MenABCWY Compared to MenACWY (Primary)

Serogroup	4-fold rate MenACWY	4-fold rate MenABCWY	NI margin	Actual margin	Power	N ABCWY/ ACWY
Family 1: NI, 2-sided score test (Miettinen and Nurminen, 1985)						
A	95%	95%	−10%	0%	99.87%	225
C	95%	95%	−10%	0%	99.87%	225
W	95%	95%	−10%	0%	99.87%	225
Y	95%	95%	−10%	0%	99.87%	225
Global Power					**99.48%**	
Family 2: NI, 2-sided score test (Miettinen and Nurminen, 1985)						
A	95%	91%	−10%	−4%	96.00%	542
C	95%	93%	−10%	−2%	99.95%	542
W	95%	91%	−10%	−4%	96.00%	542
Y	95%	93%	−10%	−2%	99.95%	542
Global Power					**91.00%**	

n = number of participants; NI = non-inferiority

Considering that approximately 10% of the selected participants might withdraw or not be evaluable for the immunogenicity objectives, the target sample size to be analyzed will be 270 participants per group and 603 participants per group for the first co-primary and the second co-primary objectives, respectively.

Evaluable means all participants included in the set for the statistical analysis defined in Section 9.3. The sample size calculation was performed in PASS 12 (Hintze, 2013). The global power for all 4 strains across Family 1 and Family 2 is the product of individual powers.

Approximately 1206 participants will be randomized in a 1:1 ratio to achieve 1084 evaluable participants (542 per group).

Withdrawals will not be replaced.

9.3 Populations for Analyses

Populations for analyses in this study are defined in Table 15.

Table 15 Populations for Analyses

Analysis set	Description
Enrolled Set (Enr)	Participant who agreed/participant for whom parent(s)/LAR(s) agreed to participate in a clinical study after completion of the informed consent process and randomized or received study intervention or undergone an invasive procedure.
Exposed Set (ES)	All participants who received at least 1 dose of the study intervention. The allocation in a group is done in function of all administered interventions.
Full Analysis Set (FAS)	All participant who received at least 1 dose of the study intervention and have post-vaccination immunogenicity data
Per Protocol Set (PPS)	All participants who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination data (FAS) minus participants with protocol deviations that lead to exclusion from the PPS.
Unsolicited Safety Set (USS)	All participants who received at least 1 dose of the study intervention (ES) that report unsolicited AEs/report not having unsolicited AEs
Solicited Safety Set (SSS)	All participants who received at least 1 dose of the study intervention (ES) that report solicited safety data

AE = adverse event; LAR = legally acceptable representative

9.3.1 Criteria for Elimination from Analysis

If the participant meets 1 of the criteria mentioned in the Section 6.8, he/she may be eliminated from per protocol analysis.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to First Participant First Visit; the SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of endpoints.

9.4.1 General Considerations

Immunogenicity:

- Non-inferiority criterion: NI will be demonstrated if, the lower limit of 2-sided 95% confidence interval (CI) for the percent difference in 4-fold rise in hSBA titers (p_MenABCWY − p_MenACWY) is above −10%, for each *N. meningitidis* A, C, W, and Y serogroup.
- Fixed sequential testing with full alpha propagation in pre-ordered hypotheses families (Family 1 and Family 2, as defined in Section 9.1) will be applied. The assay cut-off values will be defined by the laboratory before analysis and will be documented in a protocol amendment.

- For the primary and secondary endpoints, the percentages of participants with hSBA titers ≥Lower Limit of Quantitation (LLOQ) and with a 4-fold rise in hSBA titers against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W, and Y will be determined.
- For the serogroups A, C, W, Y and for each of the serogroup B indicator strains evaluation the 4-fold rise is defined as:
  - a post-vaccination hSBA titer ≥16 for participants with a pre-vaccination hSBA titer <4;
  - a post-vaccination hSBA titer ≥4 times the LLOQ for participants with a pre-vaccination hSBA titer ≥limit of detection (LOD) but <LLOQ; and,
  - a post-vaccination hSBA titer ≥4 times the pre-vaccination titer for participants with a pre-vaccination hSBA titer ≥LLOQ.
- The geometric mean titers (GMTs)/geometric mean concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log titer transformations. Values to be used for the antibody concentrations/titers below the assay cut-off will be described in the SAP.
- Handling of missing data will be discussed in the SAP.

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 will be applied. For the duration of such special circumstances, some measures may impact the data and analysis (e.g., missing visits, early study discontinuation, see Section 8.9). The impact will be determined on a case by case basis and the analysis methodology described in the SAP will account for such cases, if any.

9.4.2 Participants Disposition

The number of enrolled, vaccinated (at least 1 vaccination, full vaccination course), completed participants, screening failures, reason for withdrawal, and reason for elimination from analysis sets, as well as number of participants in FAS and PPS will be reported by group for the enrolled analysis population.

9.4.3 Primary Endpoint(s)

9.4.3.1 Immunological Non-inferiority of MenABCWY vs. MenACWY

Analysis set: The analysis of NI will be based on the PPS.

Statistical method (Family 1): For each of the serogroups A, C, W, and Y, the percentages of participants with 4-fold rise (refer to Section 9.4.1), and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each study group at 1 month after the second vaccination. The

standardized asymptotic CIs between group differences in percentages will be derived using the method of Miettinen and Nurminen (Miettinen, 1985).

NI criterion: Non-inferiority will be demonstrated if, the lower limit of 2-sided 95% CI for the percent difference in 4-fold rise in hSBA titers (p1_MenABCWY − p1_MenACWY) is above −10%, for each serogroup A, C, W, and Y.

Statistical method (Family 2): For each of the serogroups A, C, W, and Y, the percentages of participants with 4-fold rise (refer to Section 9.4.1), and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each study group at 1 month after the first vaccination. The standardized asymptotic CIs between group differences in percentages will be derived using the method of Miettinen and Nurminen (Miettinen, 1985).

NI criterion: Non-inferiority will be demonstrated if, the lower limit of 2-sided 95% CI for the percent difference in 4-fold rise in hSBA titers (p1_MenABCWY − p1_MenACWY) is above −10%, for each serogroup A, C, W, and Y.

A sensitivity analysis including minimization factors as covariates will be performed using a logistic model and will be detailed in the SAP.

9.4.3.2 Safety Analysis

Distribution of participants by vaccinations will be summarized by vaccine group for the exposed set. In case of vaccination error, participants will be analyzed “as treated” (according to the vaccine the participant actually received).

The standard coding for medical history, AE, SAE, and concomitant medications data will be done by GSK Clinical Dictionary. The coded terms received from the sponsor will be merged into the appropriate datasets before the transfer to IQVIA for statistical analyses.

9.4.3.2.1 Solicited Events

These analyses will be performed on the solicited safety set.

The frequencies and percentages of participants with solicited administration site (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) events during the 7 days (including the day of vaccination) following each vaccination at Day 1 and Day 181 will be presented.

All solicited administration site and systemic events will be summarized according to defined severity grading scales (Appendix 4). Frequencies and percentages of participants

experiencing each solicited administration site and systemic events will be presented for each symptom severity. Summary tables showing the occurrence of any solicited administration site or systemic event overall and at each time point will also be presented.

Post-vaccination solicited AEs reported from Day 1 to Day 7 will be summarized 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 summarized separately. The severity of solicited administration events, including redness at injection site, swelling of skin at injection site, and hardness of skin at injection site will be summarized according to categories described in Appendix 4.

Injection site and systemic reactions (except fever) occurring up to 7 days after each study vaccination (Day 1 and Day 181), will be summarized according to "mild", "moderate" or "severe" as described in Appendix 4.

Each solicited administration site and systemic event will also be further summarized as "none" versus "any" (for fever the latter will be ≥38.0°C/100.4°F).

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of participants reporting use.

Body temperature will be summarized by 0.5°C/32.9°F increments from 36.0°C/96.8°F up to ≥40°C/104°F and will be broken down according by route of measurement, if applicable. Frequencies and percentages of participants with temperatures ≥38.0°C/100.4°F and temperatures ≥40.0°C/104°F will also be presented.

9.4.3.2.2 Unsolicited AEs

These analyses will be performed on the unsolicited safety set.

The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs [see all relevant AE definitions in Appendix 1, Glossary of Terms]) during the 7 and the 30 days (including the day of vaccination) following vaccination at Day 1 and Day 181 will be presented.

The frequencies and percentages of participants with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period will be presented.

This analysis applies to all AEs occurring during the study, judged either as probably related, possibly related or not related to vaccination by the investigator, recorded in AE eCRF, with a start date on or after the date of first vaccination (Table 12). AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The AEs will

then be grouped by MedDRA PTs into frequency tables according to system organ class (SOC).

All reported AEs, as well as AEs judged by the investigator as related to study vaccine, will be summarized according to SOC and PT within SOC. These summaries will be presented by vaccine group and by interval of study observation. When an AE occurs more than once for a participant, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- SAE
- AE related to vaccine
- AESI
- AE leading to withdrawal
- AE leading to a medically attended visit

Data listings of all AEs will be provided by participant. In addition, AEs in the categories above will be provided as listed data.

9.4.4 Secondary Endpoints

9.4.4.1 Immune Response N. Meningitidis Serogroups A, C, W, and Y (Measured by hSBA)

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

Statistical method: For each of the 4 *N. meningitidis* serogroups A, C, W, and Y the percentages of participants with hSBA titers ≥LLOQ and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for ABCWY and ACWY study groups. Refer to Section 9.4.3.1 for the definition of 4-fold rise for the Men A, C, W, and Y evaluation.

Geometric mean titers and associated 2-sided 95% CIs will be computed for each group and for each strain at each visit. The titers at baseline (Day 1, Month 0), at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group, and at 1 month after the single MenACWY vaccination (Day 31, Month 1) in the ACWY group, will be logarithmically transformed (base10) to fulfill the normal distribution assumption.

Geometric mean titers and 95% CIs will be calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 95% CIs of the log-transformed titers (base10) obtained from a 2-way Analysis of covariance (ANCOVA) with factors for vaccine group and country. The ANCOVA will include baseline titers as covariate, and it will be performed to take into consideration the possible effect of these on the post-vaccination titers.

Geometric mean ratios (GMRs) (post-vaccination/baseline titer) and associated 2-sided 95% CIs will be computed for each group and for each strain at each visit. Geometric mean ratios will be calculated by exponentiating (base10) the least squares means and the lower and upper limits of the 95% CIs of the log-transformed titers (base10) obtained from a 2-way ANOVA with factors for vaccine group and country.

Additionally, GMTs and GMRs group ratios between the 2 intervention groups and their respective 95% CIs will be computed by exponentiating the difference of the least square means of the log-transformed titers and the lower and upper limits of the 95% CIs on the difference obtained from the ANCOVA/ANOVA model above.

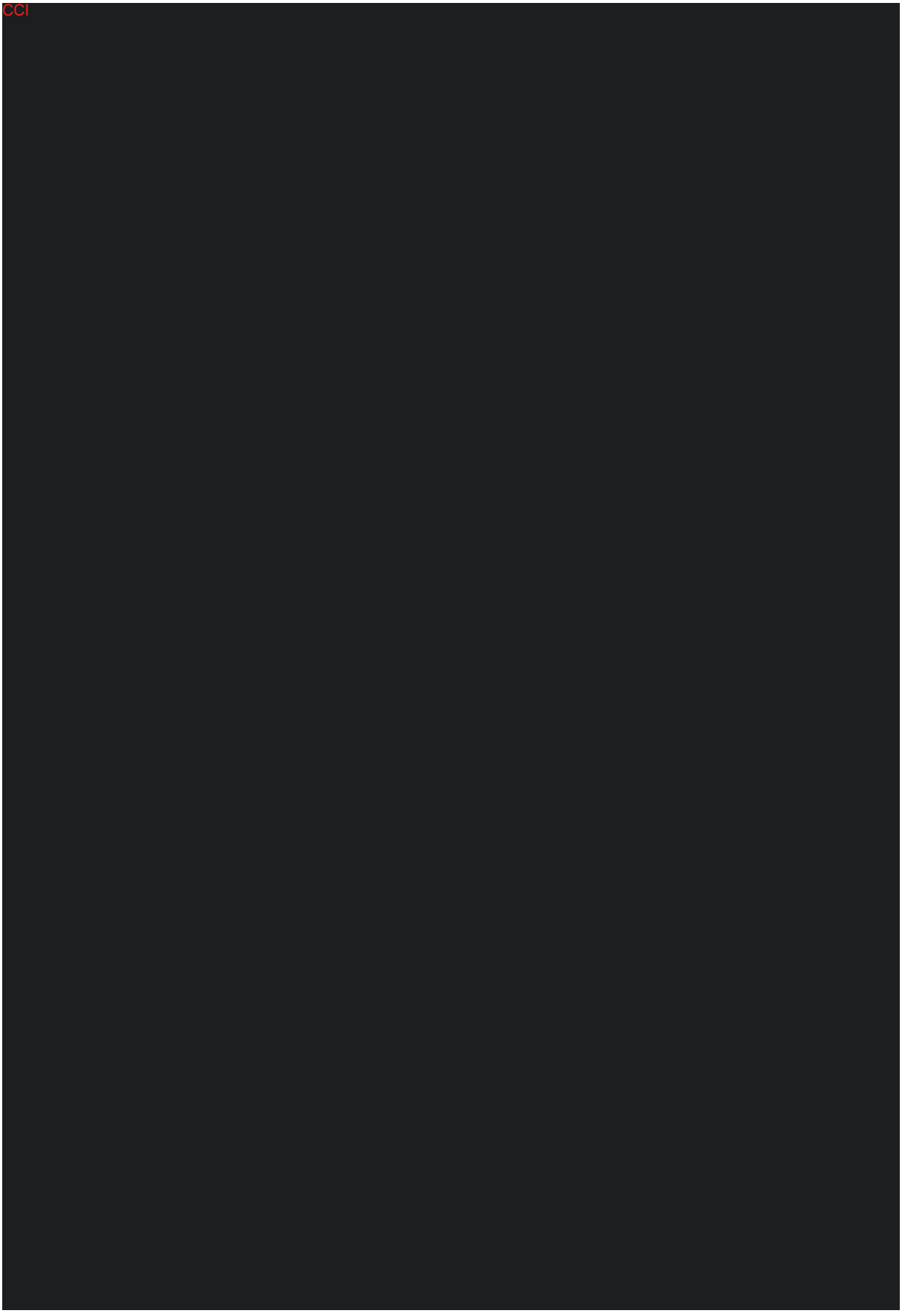
9.4.4.2 Immune Response – *N. Meningitidis* Serogroup B Indicator Strains (Measured by hSBA)

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

Statistical method: For each of *N. meningitidis* B indicator strain (M14459 for factor H binding protein [fHbp] antigen, M13520 for Neisseria Heparin Binding Antigen (NHBA) antigen, 96217 for Neisseria adhesin A (NadA) antigen and NZ98/254 for PorA P1.4 antigen) the percentages of participants with hSBA titers ≥LLOQ and of participants with 4-fold rise (refer to Section 9.4.1), and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for MenABCWY study group at 1 month after the last MenABCWY vaccination .

A composite endpoint defined as the percentage of participants with hSBA titers ≥LLOQ for all (4) *N. meningitidis* B indicator strains will be derived. For this composite endpoint, the percentage of participants with hSBA titers ≥LLOQ for all (4) B indicator strains and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for MenABCWY study group at 1 month after the last MenABCWY vaccination.

Geometric mean titers and GMRs, and associated 2-sided 95% CIs will be computed for each strain at each visit. The hSBA titers at baseline (Day 1, Month 0), and the hSBA titers at 1 month after the last vaccination (Day 211, Month 7) for the ABCWY group, will be logarithmically transformed (base10) to fulfill the normal distribution assumption.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9.4.6 Other Analyses

No other analyses are planned.

9.4.6.1 Demography and Baseline Characteristics Analyses

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

Distributions of participants by sex, race, and ethnic origin will be summarized overall and by vaccine group.

Demography will be done for the FAS and PPS.

9.5 Interim Analyses

An interim analysis of safety objectives may be conducted after at least 50% of participants have completed Visit 4. An interim analysis of immunological objectives may also be performed after all participants have completed Visit 4. If performed, the assessment of the primary immunological objectives will follow the order described in Section 9.4.3.1 with analysis of family 1 preceding that of family 2. The final study report will contain the final analyses of all primary and secondary endpoints and made available to the investigators.

9.5.1 Sequence of Analyses

The interim analysis for the evaluation of the co-primary objectives will respect the hierarchical order described in Section 9.4.3.1.

9.5.2 Statistical Consideration for Interim Analysis

No changes in statistical methodology for the immunological and safety objectives are foreseen compared to what is planned for the final analysis.

Data for the interim analysis may be analyzed by an independent unblinded group; if so, only group unblinded results will be presented.

9.6 Data Monitoring Committee

Not applicable.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations and Glossary of Terms

Abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
ADE	Adverse device effect
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CFR	Code of Federal Regulations
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
COVID-19	Coronavirus disease 2019
CRM	Cross-reacting Material
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture System
eDiary	Participant Diary (Electronic Diary)
ES	Exposed Set
ELISA	Enzyme-linked immunosorbent assay
Enr	Enrolled Set
EoS	End of Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
fHbp	Factor H binding protein
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMR	Geometric mean ratio
GMT	Geometric mean titer
GSK	GlaxoSmithKline
HRT	Hormone replacement therapy
hSBA	Human Serum Bactericidal Assay
IB	Investigator’s Brochure

Abbreviation	Definition
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMD	Invasive meningococcal disease
IND	Investigational New Drug
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LAR	Legally acceptable representative
LLOQ	Lower limit of quantitation
LOD	Limit of detection
LSLV	Last Participant Last Visit
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
MenABCWY	Meningococcal serogroups A, B, C, W, and Y investigational vaccine
MenACWY	Meningococcal serogroups A, C, W, and Y conjugate vaccine
MenB	Meningitis B
NadA	Neisseria adhesin A
NHBA	Neisseria Heparin Binding Antigen
NI	Non-inferiority
NZ	New Zealand
OMV	Outer membrane vesicles
PCD	Primary completion date
pIMD	Potential immune-mediated disease
PT	Preferred term
PorA	Porin A
PPS	Per Protocol Set
SADE	Serious adverse device effect
SAE	Serious adverse event
SoA	Schedule of Activities
SOC	System organ class
SSS	Solicited Safety Set
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Definition
T	Telephone contact
USADE	Unexpected serious adverse device effect
US	United States (of America)
USS	Unsolicited Safety Set
V	Visit

Glossary of Terms

Term	Definition
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, 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 participant, the study center and sponsor or sponsor's designee's personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.
Caregiver	A "caregiver" is someone who lives in the close surroundings of a participant and has a continuous caring role or has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.
Child in care	A child who has been placed under the control or protection of an agency, organization, 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.
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 (participant)	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled (participant)	"Enrolled" means a participant's/participant's parent(s)'/LAR(s)' agreement to participate in a clinical study following completion of the informed consent process. Potential participants 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 the Section 9.3 for the definition of "enrolled" 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.
Evaluable (participant)	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis. Refer to Section 9.3 for details on criteria for evaluability.
Immunological correlate of protection	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention	Term used throughout the clinical study to denote a set of investigational product or marketed product or placebo intended to be administered to a participant.
Investigational vaccine/product	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization 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 study at a study center. If a study is conducted by a team of

	individuals at a study center, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study center to qualified individual or party to perform those study-related duties and functions.
Interactive voice response system (IVRS)	The software that enables the randomizing of participants into clinical trials and allocation of the study product to them in a blinded fashion. This technology allows study centers to interact with a database by pressing keypad buttons on a phone and following voice prompts in order to enter in information.
Legally acceptable representative	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study. The terms legal representative, legally authorized representative are used in some settings.
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.
Medically attended AEs	Symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.
Study/Site Monitor	An individual assigned by the sponsor or sponsor's designee and responsible for assuring proper conduct of clinical studies at 1 or more study centers. The terms Clinical Research Monitor and Clinical Research Associate are used in some settings.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the vaccine(s)/product or as a control. Synonym: participant
Participant number	A unique identification number assigned to each participant who consents to participate in the study.

Primary completion date (PCD)	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical study 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 participants, scope of the investigation, study design, or scientific integrity of the study.
Qualified health care professional	Term used to refer to any licensed or certified health care professional who is permitted by institutional policy to perform protocol required procedures, and who is identified within the Study Staff Signature Log.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study	Study with objectives not linked to the data of another study.
Solicited event	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant 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 study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). A certified copy is 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.
Source documents	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' 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, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).
Study vaccine/product	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical study that evaluates the use of an investigational vaccine/product.
Treatment	Term used throughout the clinical study to denote a set of investigational product or marketed product or placebo intended to be administered to a participant.
Treatment number	A number identifying intervention given to a participant, according to intervention allocation.
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 AE.
Witness (impartial witness)	The witness is an individual independent of the study, whose role is to attend the informed consent process if the participant/participant's parent(s)/LAR(s) cannot read. The witness reads the documents supplied to the participant/participant's parent(s)/LAR(s) and signs them after the participant/participant's parent(s)/LAR(s) sign/thumb print the applicable documents. The witness cannot in any way influence participant's/participant's parent(s)'/LAR(s)' decision to participate in the study.

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

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 GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF and Informed Assent Form (IAF) if applicable, IB, 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 protocol amendments 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 participants.
- IQVIA 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/IEC.
  - 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 study center and adherence to requirements of Code of Federal Regulations Title 21 (21 CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each investigator will sign the protocol signature page (Appendix 8) and send a copy of the signed page to IQVIA. The study will not start at any study center at which the investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-investigators will provide IQVIA with sufficient, accurate financial information as requested to allow the sponsor or IQVIA to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing financial interest information prior to initiation

of the study center. Investigators are responsible for providing the financial information update if their financial interests change at any point during their participation in a study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the participants in this study. The terms of the insurance will be kept in the study files.

Informed Consent and Assent Process

- The investigator or his/her representative will explain the nature of the study to the participant/participant's parent(s)/LAR(s) and answer all questions regarding the study.
- Participant/participant/s parent(s)/LAR(s) must be informed that their participation is voluntary. Participants/participants' parents/LARs will be required to sign a statement of informed consent or assent (if applicable) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC.
- The medical record must include a statement that informed consent and assent (if applicable) was obtained before the participant was enrolled in the study and the date the written consent and assent (if applicable) was obtained. The authorized person obtaining the informed consent and assent (if applicable) must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) and assent form(s) during their participation in the study.
- A copy of the ICF(s) and assent form(s) (if applicable) must be provided to the participant participants' parent(s)/LAR(s).
- Re-consent must be obtained in accordance with local laws and regulations for participants who become legally emancipated during the study, i.e. reach the legal age of consent. The participant can provide consent by signing/witnessing/thumb printing an ICF, similar to that provided to the parent(s)/LAR(s) at study start, which summarizes the study and includes a consent statement and documents that the participant agrees to continue participating in the study.

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 GCP E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IEC/IRB must be given to IQVIA 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 the Medical Monitor, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IEC/IRB, and regulatory authorities as required. If an inspection of the study center is requested by a regulatory authority, the investigator must inform IQVIA 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 participants 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, and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of participants experiencing any adverse event related to the study.
- If permission to do so is given by the participant and/or participant's parent(s)/LAR(s), ensuring that the participant's primary health care provider is informed of the participant'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/favorable opinion from the IEC/IRB of an amendment, except where necessary to eliminate an immediate hazard to study participants, or when the change involves only logistical or administrative aspects. 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 participants without prior IEC/IRB approval/favorable 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:

- to the IEC/IRB for review and approval/favorable opinion,
- to the sponsor for agreement and, if required,
- to the regulatory authority(ies).

Administrative Structure

Table 16 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Medical Monitoring, Study Master File	IQVIA
Randomization, Blinding, Unblinding	Cenduit
Clinical Supply Management, Quality Assurance Auditing	GSK
Biostatistics, Medical Writing	IQVIA
Laboratory Assessments	GSK

Medical Monitor

Refer to the study reference manual.

Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study register in compliance with the applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. IQVIA 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 participants, as appropriate.
- IQVIA will provide the investigator with the randomization codes for their study center only after completion of the full statistical analysis.
- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

Data Quality Assurance

- The investigator should maintain a record of the location(s) of their respective essential documents including source documents (see Appendix 1, Glossary of Terms, for definitions of essential documents and source documents). The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.
- Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, eCRF), the copy should fulfill the requirements for certified copies.
- All participant data relating to the study will be recorded on eCRF (or printed CRF in case of an electronic data capture system [EDC] failure) unless transmitted to the sponsor or IQVIA electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's participants that supports 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.
- IQVIA is responsible for the data management of this study including quality checking of the source data.
- Study/Site Monitors (see a definition in Appendix 1, Glossary of Terms) will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center 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). The safety and rights of participants 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.
- Study records and source documents, including signed ICF/IAF (as applicable), pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final 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 from the sponsor. No records may be transferred to another location or party without written notification to the sponsor or IQVIA.

Source Documents

- Source documents provide evidence for the existence of the participant 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 Appendix 1, Glossary of Terms.

Study and Study Center Closure

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

The investigator may initiate study center 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 center by IQVIA/GSK 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 participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, IQVIA shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, for the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

Publication Policy

The sponsor aims to submit for publication the results of the study in searchable, peer reviewed scientific literature within 18 months from LSLV for interventional studies and follows authorship and other guidance from the International Committee of Medical Journal Editors.

Appendix 3 Clinical Laboratory Tests

Protocol-required Safety Laboratory Assessments

A urine pregnancy test will be conducted as needed for women of childbearing potential.

Laboratory Assays

MenACWY Serum Bactericidal Assays Using Human Complement (hSBA)

The induction of functional anti-meningococcal activity by bactericidal antibodies directed against *N. meningitidis* serogroups A, C, W, and Y will be also determined by hSBA using a new format, so-called agar overlay hSBA, using a higher throughput colony counting method compared to the manual hSBA based on the Tilt method.

This new hSBA is also 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 titer 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 (AxioLab Image Analysis System – detection of colony-forming units).

MenACWY IgG ELISA

- The anti-MenACWY total IgG antibody 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.

MenB Serum Bactericidal Assays Using Human Complement (hSBA)

Serum bactericidal activity against MenB 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 bactericidal 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.

CCI

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of AEs

Adverse Events

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. 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 study intervention.

Events <u>Meeting</u> 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 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 or a concurrent medication (overdose per se should not be reported as an AE/SAE). • Signs or symptoms temporally associated with study vaccine(s)/product administration. • Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits). • Significant failure of an expected pharmacologic or biological action. • Pre- or post-intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen). • 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. • AEs will be recorded as solicited AEs if they do not meet the definition of unsolicited AEs. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT Meeting</u> 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 participant prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to

informed consent signature) that did not worsen from baseline.

- Clinically significant abnormal laboratory findings or other abnormal assessments that are present or detected at the start of the study and do not worsen.

Serious Adverse Events

An 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 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, had it been more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

Note: In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are also considered as AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will also be considered serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

d) Results in disability/incapacity

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, diarrhea, 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 participant

f) Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).

g) Other situations

Medical or scientific judgment 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 hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 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 hospitalization.

Solicited Events

Solicited Events will include the following:

a) Solicited administration site events

The following administration site events will be solicited for **all age groups**:

- Pain
- Redness
- Swelling
- Induration

Solicited Events will include the following:
Note: participants/participants' parents/LARs will be instructed to measure "Solicited administration site events" using the ruler provided by the site. Should multiple measurements be performed during the day, participants/participants' parent(s)/LAR(s) will be instructed to record the highest grading in the eDiary.
b) Solicited systemic events The following systemic events will be solicited **for adults 15 to 25 years**: • Fever • Fatigue • Nausea • Headache • Arthralgia • Myalgia Note: participants/participants' parents/LARs will be instructed to measure and record the preferably oral body temperature in the evening using the thermometer provided by the site. Should additional temperature measurements be performed at other times of day, participants/participants' parents/LARs will be instructed to record the highest temperature in the eDiary. Note: Any solicited event that meets any of the following criteria must be entered into the participant's source documents and eCRF: • Solicited administration site or systemic event that leads to a visit to a health care provider (medically attended AE). • Solicited administration site or systemic event leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal). • Solicited administration site or systemic event that otherwise meets the definition of an SAE.

Unsolicited AEs

Definition of an Unsolicited AE:
An unsolicited AE is an AE that was not solicited using an eDiary and that was spontaneously communicated by a participant/participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants/participants' parents/LARs will be instructed to contact the study center as soon as possible to report medically attended events, as well as any events that, though not medically attended, are of participant/parental/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified study center personnel and documented in the participant's records. Unsolicited AEs that are not medically attended nor perceived as a concern by participant/participant's parent(s)/LAR(s) will be collected during interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

COVID-19 Cases

Diagnosis of COVID-19 should be made in accordance with the WHO case definition. Cases should be categorized as AEs or SAEs, and routine procedures for recording,

evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in the protocol (Table 12, Table 13).

Adverse Events of Special Interest (AESIs)

Definition of an AESI
Adverse events of special interest (AESIs) are predefined (serious or non-serious) AEs 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 characterize and understand it.

Potential Immune-Mediated Diseases (pIMDs)

Potential immune-mediated diseases 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 etiology. Adverse events that need to be recorded and reported as pIMDs include those listed in the Table 17.

However, the investigator will exercise his/her medical and scientific judgment to determine 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.

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

Table 17 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 such as 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, – Dermatitis herpetiformis. • Lichen planus. • Sweet's syndrome. • Localised scleroderma (morphoea).
Vasculitis	**Blood Disorders**	**Others**
• Large vessels vasculitis including: – Giant cell arteritis (temporal arteritis),	• Autoimmune haemolytic anemia. • Autoimmune thrombocytopenia.	• Autoimmune glomerulonephritis including: – IgA nephropathy,

– 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.	• Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	– 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.

Other AEs of Special Interest

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.

Arthritis

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

- Presence of physical examination findings of swelling, redness, heat, or limitation in range of motion

and/or

- Presence of 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 Standardized MedDRA Queries (SMQ) Narrow "Arthritis". For any new diagnosis of arthritis (serious or non-serious) in a study participant, the investigator (or designate) must complete an electronic Expedited Adverse Events Report and an ad-hoc eCRF page on arthritis to further characterize this AESI.

Clinical Laboratory Parameters and Other Abnormal Assessments Qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments the investigator considers clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE.

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

Events or Outcomes Not Qualifying as AEs or SAEs

Pregnancy

Female participants who become pregnant after the first vaccination must not receive subsequent doses of the study vaccine(s)/product, but may continue other study procedures at the discretion of the investigator.

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

Recording and Follow-up of AEs, SAEs, AESIs, and Pregnancies

AE and SAE Recording
• The participants/participants' parents/LARs will be instructed to contact the investigator immediately should the participants manifest any signs or symptoms they perceive as serious. • 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 participant's medical records to neither the sponsor nor IQVIA instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor or IQVIA. In this instance, all participant identifiers will be blinded on the copies of the medical records prior to submission to the sponsor or IQVIA. • 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. • An eDiary will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete each field of the eDiary. • Any individual(s) who perform the measurements of administration site or systemic events and who will enter the information into the eDiary should be trained on the use of the eDiary. This training must be documented in the participant's source record. If any other individual other than the participant/participant's parent(s)/LAR(s) is making entries in the eDiary, their identity should be documented in the participant's source record. • Refer to the study reference manual for more information regarding the use of eDiary.

Time Period for Collecting and Recording AEs, SAEs, AESIs, and Pregnancies
All solicited events that occur during 7 days following administration of each dose of study vaccine(s)/product (including the day of vaccination) (Day 1 and Day 181) must be recorded into the eDiary, irrespective of intensity. All other AEs occurring within the time frame described in Table 12 should be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related. Refer to Section 8.3.6.1 for collecting and reporting of safety information.

Follow-up of AEs, SAEs, AESIs, Pregnancies, or any Other Events of Interest

After the initial AE/SAE/AESI/pregnancy or any other event of interest for the study, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until the last contact or until the participant is lost to follow-up.

Follow-up During the Study

AEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit/contact of the participant.

If the participant dies during participation in the study or during a recognized follow-up period, IQVIA will be provided with any available post-mortem findings, including histopathology.

Follow-up After the Participant is Discharged From the Study

The investigator will provide any new or updated relevant information on previously reported SAE/AESI to IQVIA using electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

Follow-up of Pregnancies

Pregnant participants 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 IQVIA 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 an SAE, it should always be reported as SAE.

Furthermore, in case if the investigator becomes aware of 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, he/she has to report this information to IQVIA as described in Section 8.3.6.4.

Updating of SAE, AESI, and Pregnancy Information After Removal of Write Access to the Participant's eCRF

When additional SAE, AESI, or pregnancy information is received after removal of write access to the participant's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to IQVIA as described in the relevant section within the timeframes specified in Table 13).

Assessment of Intensity

Maximum Intensity for Solicited Events

The intensity of the following solicited AEs will be assessed as described in the table below.

Intensity Scales for Solicited Events in Adults and Children of 6 Years of Age or Older

Adults/Child (≥10 years)		
Event	**Intensity Grade**	**Parameter**
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday

		activities.
Redness at administration site		Record greatest surface diameter in mm
Swelling at administration site		Record greatest surface diameter in mm
Induration at administration 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

*Refer to the SoA (Table 3) for the definition of fever and the preferred location for temperature measurement

Maximum Intensity of Local Injection Site Redness/Swelling/Induration

The maximum intensity of local injection site redness/swelling/induration and fever will be scored as follows:

	Redness/swelling/induration	**Fever**
0:	1 to 24 mm	<38.0°C (100.4°F)
1:	25 to 50 mm	≥38.0°C (100.4°F) to ≤38.9°C (102.1°F)
2:	51 to 100 mm	>39.0°C (102.2°F) to ≤39.9°C (103.9°F)
3:	>100 mm	>40.0°C (104°F)

Maximum Intensity for Unsolicited AEs and SAEs

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

judgment.

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

- 1 (mild): An AE which is easily tolerated by the participant, 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/daycare 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 an 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 outcomes that define an SAE.

Assessment of Causality

All solicited administration-site and systemic events will be considered causally related to vaccination.

The investigator must assess the relationship between study vaccines and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different vaccines/products were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (ie investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all products.

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

Causality should be assessed by the investigator using the following question:

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

- YES: There is a reasonable possibility that the study vaccine(s)/product 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. There are other, more likely causes and administration of the study vaccine(s)/product is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as "serious", additional examinations/tests will be performed by the investigator 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, if applicable.
- Erroneous administration.
- Other cause (specify).

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to IQVIA. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to IQVIA.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

Medically Attended Visits
For each solicited and unsolicited symptom the participant experiences, the participant/participant's parent(s)/LAR(s) will be asked if he/she/the participant received medical attention defined as hospitalization, 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.

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).

Reporting of SAEs, AESIs, Pregnancies, and Other Events

Events Requiring Expedited Reporting to IQVIA
• Once an investigator becomes aware that an SAE/AESI has occurred in a study participant, the investigator or investigator's designee must complete information in the electronic Expedited AE Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. The report allows to specify that the event is an AESI and whether it is serious or non-serious. • Even if the investigator does not have all information regarding an SAE/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 SAE/AESI causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the SAE/AESI. • Refer to Table 13 for the details on timeframes for reporting of SAEs/AESIs and pregnancies

SAE/AESI/Pregnancy Reporting to IQVIA via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE/AESI/Pregnancy to IQVIA will be an EDC. • If the EDC is unavailable for more than 24 hours, then the study center will use the paper Expedited AE/Pregnancy Report (see details in the next section). • The study center will enter the SAE/AESI/pregnancy data into the EDC as soon as it become available. • After the study is completed at a given study center, the EDC will be taken offline to prevent the entry of new data or changes to existing data. • If a study center receives a report of a new SAE/AESI/pregnancy from a participant or receives updated data on a previously reported SAE/AESI/pregnancy after the EDC has been taken offline, then the study center can report this information on a paper Expedited AE/Pregnancy Report (see the next section) or to the Medical Monitor by telephone. • Contacts of the Medical Monitor for SAE/AESI/pregnancy reporting can be found in the study reference manual.

Back-up SAE/AESI/Pregnancy Reporting to IQVIA via Paper (in Case of EDC Failure)
• Facsimile transmission (fax) of the SAE/AESI/pregnancy paper Expedited AE/Pregnancy Report in case of EDC failure is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of a fax equipment, notification by telephone is acceptable with a copy of the paper Expedited AE/Pregnancy Report sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Expedited AE/Pregnancy Report within the designated reporting timeframes. • Contacts of the Medical Monitor for SAE/AESI/pregnancy reporting can be found in the study reference manual.

Definitions of Medical Device Adverse Events and Adverse Device Effects

A Medical Device AE is:
is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to a medical device. 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:
Any 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.

Definitions of a Medical Device SAE, Serious Adverse Device Effect, and Unexpected Serious Adverse Device Effect

A Medical Device SAE is Any SAE 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 hospitalization. Planned hospitalization 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

A Serious Adverse Device Effect (SADE) is:
• A SADE is defined as an ADE 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, intervention had not occurred, or circumstances had been less fortunate.
An Unanticipated SADE (USADE) is:
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a SADE that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.

Recording and Reporting of Medical Device AE, ADEs, SADEs and USADE
• Any device deficiency must be reported to IQVIA within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • E-mail/fax transmission of the paper "Medical device or combination product with device deficiency/incident report form" is the preferred method to transmit this information to IQVIA. • 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 of the Medical Monitor for medical device safety events reporting can be found in the study reference manual. • IQVIA will review all device deficiencies and 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.

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential

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

Women NOT Considered as Women of Childbearing Potential

1. Premenarchal female*:
   a) Menarche is defined as an 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.
   b) If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy
   Note: Documentation can come from the study center staff: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
   b) 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 enrollment.

**Note: If the childbearing potential changes after start of the study (e.g., a premenarchal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.*

Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in the sponsor's list of highly effective contraceptive methods provided in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent*   *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   • Oral   • Injectable
Highly Effective Methods That Are User Independent*
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation   • Intrauterine device   • Intrauterine hormone-releasing system   • Bilateral tubal occlusion
Vasectomized partner   *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant,   *(The information on the male sterility can come from the study center personnel's review of the participant'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 participant.)*

* 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 participants in clinical studies.

Female participants must practice adequate contraception for 30 days prior to vaccination, have a negative pregnancy test on the day of vaccination, and agree to continue adequate contraception during the entire intervention period and for 30 days after completion of the vaccination series.

Female Participants Who Become Pregnant

Refer to the Sections 8.3.6 for information on detection, recording, reporting and follow-up of pregnancies. Any female participant who becomes pregnant during the study will discontinue study intervention. For a participant who becomes pregnant during the study, this information will be shared with the participant's parent(s)/LAR(s) depending on the participant's age as required by local regulations.

Appendix 6 Country-specific Requirements

To be confirmed.

Appendix 7 Protocol Amendment History

See the Summary of Changes for Protocol Amendment 3 directly before the Table of Contents.

The history of Amendments 1 and 2 is provided below.

Amendment 2 – 12 February 2021

This amendment was considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 2:

The primary goal of Amendment 2 was to promote one of the secondary endpoints to co-primary, which would allow to evaluate vaccine immunogenicity at 1 month after both the first and the second MenABCWY vaccinations (0,6-months). Also, considering that some of the study interventions are combination products constituted of a device and biologic product (pre-filled syringes), the amended protocol provided instructions for collection of safety information related to the use of medical devices.

Description of Changes in Amendment 2:

<table>
<tr><th>Section # and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td colspan="3">Substantial Changes</td></tr>
<tr><td>1.1 Synopsis</td><td>The following secondary endpoint was promoted to co-primary and labeled “Family 1”:
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Immunological non-inferiority: MenABCWY vs. MenACWY (Family 1):
To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against N. meningitidis serogroups A, C, W, and Y, at 1 month after the second MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).</td><td>The percentages of participants with a 4-fold rise in hSBA titers against N. meningitidis serogroups A, C, W, and Y at 1 month after the second vaccination for the ABCWY group (Day 211, Month 7), and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).</td></tr>
</table>
The original primary endpoint was changed to co-primary and was labeled “Family 2”:
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
</table></td><td>To promote one of the secondary endpoints to co-primary, which will allow to evaluate vaccine immunogenicity at 1 month after both the first and the second MenABCWY vaccinations (0, 6-months)</td></tr>
</table>

Section # and Name	Description of Change		Brief Rationale
	Immunological non-inferiority: MenABCWY vs. MenACWY (Family 2) To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the first MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	The percentages of participants with a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the first vaccination for the ABCWY group (Day 31, Month 1), and 1 month after the single dose of MenACWY vaccination for the ACWY group (Day 31, Month 1), relative to baseline (Day 1, Month 0).	
1.3 Schedule of Activities	In the footnote for Table 3 (formerly Table 1 in the original protocol) "Schedule of Activities", the following footnotes were added: [1] Home visits are always allowed if deemed suitable and are conducted according to local regulations.		To allow additional flexibility to perform study visits.
	[9] Frequency or urine pregnancy tests can be established at the site according to local regulations. Numbering of the footnotes shifted accordingly. The cross-reference to the footnote 1 was added to the row "Days post-vaccination" The cross-reference to the footnote 9 was added to the row "Urine		To reflect local requirements on pregnancy testing.

<table>
<tr><th>Section # and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>pregnancy test for females of childbearing potential”</td><td></td></tr>
<tr><td>3.0 OBJECTIVES AND ENDPOINTS</td><td>Table 6 “Study Objectives and Endpoints” was revised to reflect the changes made in the same table in Synopsis.</td><td>For consistency.</td></tr>
<tr><td rowspan="2">5.1 Inclusion Criteria</td><td>The following text was revised as follows (the new text is bold):
4. Previous vaccination with 1 dose of MenACWY vaccine at an age of 10 years or older, with an interval of at least 4 years and not more than 6 years (intended as up to 6 years and 364 days) between the previous MenACWY vaccine and enrollment (informed consent and assent [as applicable]) into this study.</td><td>For clarity.</td></tr>
<tr><td>The following sentence was added:
Frequency or urine pregnancy tests can be established at the site according to local regulations.</td><td>To incorporate local requirement on pregnancy testing.</td></tr>
<tr><td>5.2.1 Medical Conditions
5.2.2 Prior/Concomitant Therapy</td><td>The exclusion criteria #7 and #14 were revised as follows (the new text is bold; the deleted text is crossed out):
<s>For corticosteroids (oral/intravenous/intramuscular), with mean prednisone ≥20 mg/day (for adult participants), or ≥0.5 mg/kg/day, or ≥20 mg/day whichever is the maximum dose for pediatric participants, or equivalent.</s>
For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants and ≥0.5 mg/kg/day with maximum ≥20 mg/day for pediatric participants.</td><td>For clarity.</td></tr>
<tr><td>6.1 Study Interventions Administered</td><td>In Table 8 (formerly Table 6) “Study Interventions Administered”, the following rows (shown in bold) were added:
<table>
<tr><td>Study Interventio</td><td>MenABCWY</td><td>Menveo</td><td>Bexsero</td><td>Placebo</td></tr>
</table>
</td><td>The new row with “Product type” was added to identify combination products.</td></tr>
</table>

<table>
<tr><th>Section # and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>
<table>
<tr><td>n Name</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Product type</td><td>Combination</td><td>Biological</td><td>Combination</td><td>Combination</td></tr>
<tr><td>Type</td><td>Study</td><td>Control</td><td>Additional</td><td>Additional</td></tr>
</table>
</td><td></td></tr>
<tr><td>6.3.5.1 Blinding</td><td>The following text was revised as follows (the new text is bold; the deleted text is crossed out):
<s>The laboratory in charge of the sample testing will be blinded to the intervention assignment. Codes will be used to link the participant and study (without any link to the intervention attributed to the participant) to each sample.</s>
The laboratory in charge of the laboratory testing will be blinded to the treatment, subject and visit number, and codes will be used to link the subject, visit and study (without any link to the treatment attributed to the subject) to each sample.</td><td>For clarity.</td></tr>
<tr><td>6.7 Criteria for Temporary Delay for Enrollment and/or Vaccination and/or Blood Sampling</td><td>The following text was revised as follows (the new text is bold):
Under such circumstances, a participant may be considered eligible for study enrollment and/or vaccination after the appropriate window for delay described above, or as defined by local health authorities, has passed and inclusion/exclusion criteria have been re-checked, and if the participant is confirmed to be eligible.</td><td>For clarity.</td></tr>
<tr><td>8.1.2 Laboratory Assays</td><td>In the footnote for Table 10 (formerly Table 8) “Laboratory Assays”, the text was revised as follows (the added text is bold; the deleted text is crossed out):</td><td>To reflect the fact that Nexelis acquired CLS in Germany.</td></tr>
</table>

Section # and Name	Description of Change	Brief Rationale
	GSK Biologicals 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 Siena, Italy, **or to Nexelis in Marburg, Germany,** or to ~~an~~ other external laborator~~y~~**ies**.	
8.3.6.1 Time Period and Frequency for Collecting AE and SAE Information	The following text was added: 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).	For clarity and to align with other MenABCWY protocols
8.3.8 Medical Device Deficiencies	The new section "Medical Device Deficiencies" was added, with the following subsections included (*only the subsections headers are shown; see the content of these sections in the body of the protocol amendment*): **8.3.8.1 Detection, Follow-up and Prompt Reporting of Medical Device Deficiency** **8.3.8.2 Regulatory Reporting of Medical Device Deficiency When Used as Combination Product**	Given that the study interventions (MenABCWY and *Bexsero*) are combination products constituted of a device and biologic product (pre-filled syringes), the language regarding combination products, collection and reporting of safety events related to medical devices in accordance with the FDA guidelines, was added.
9.1 Statistical Hypotheses	The text was revised as follows *(the added content is bold; the deleted text is crossed out):*	Statistical considerations were revised to accommodate

	First Co-Primary Immunogenicity Objective **(Family 1)** The **first co-**primary immunogenicity objective is to demonstrate the immunological non inferiority (NI) of the antibody response to MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with MenACWY, as measured by percentage of participants with 4-fold rise in hSBA titer against each of the N. meningitidis serogroups A, C, W, and Y, at 1 month after the ~~first~~ **second** MenABCWY vaccination and 1 month after the MenACWY vaccination (single dose). This translates to the following hypotheses: H_0: (p1_MenABCWY(i) – p1_MenACWY(i) ≤−10% vs. H_1: (p1_MenABCWY(i) – p1_MenACWY(i) >−10% Where p1_MenABCWY(i) denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the ~~first~~ **second** vaccination of MenABCWY group and p1_MenACWY(i) denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the single vaccination of MenACWY group. **NI criterion: Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the percent difference in the 4-fold rise in hSBA titers (p_MenABCWY– p_MenACWY) is above −10% for each serogroup A, C, W, and Y.** **Second Co-Primary** ~~Secondary~~ Immunogenicity Objective **(Family 2)** The second~~ary~~ **co-primary** immunogenicity objective is to demonstrate the immunological NI of the antibody response to MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with MenACWY, as measured by percentage of participants with 4-fold rise in hSBA titer against each of the *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the ~~second~~ **first** MenABCWY vaccination and 1 month after the MenACWY vaccination (single dose). This translates to the	additional analyses required in the study due to promotion of one of the secondary endpoints to co-primary. Identifiers “Family 1” and “Family 2” were added for referencing testing strategy for the 2 co-primary endpoints.

<table>
<tr><th>Section # and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>following hypotheses:
H_0: (p2_MenABCWY(i) – p2_MenACWY(i) ≤−10%
vs.
H_1: (p2_MenABCWY(i) – p2_MenACWY(i) >−10%
Where p2_MenABCWY(i) denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the ~~second~~ first vaccination of MenABCWY group and p2_MenACWY(i) denotes the percentages of participants with 4-fold rise in hSBA titers for serogroups i=A, C, W, and Y, 1 month after the single vaccination of MenACWY group.
NI criterion: Non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI for the percent difference in the 4-fold rise in hSBA titers (p_MenABCWY– p_MenACWY) is above −10% for each serogroup A, C, W, and Y.</td><td></td></tr>
<tr><td>9.2 Sample Size Determination</td><td>The text was revised as follows (the added content is bold; the deleted text is crossed out):
~~Table 14 Power to Demonstrate Immunological Non-inferiority for Serogroups A, C, W, and Y of MenABCWY Compared to MenACWY (Primary)~~
<table>
<tr><th>~~Serogroup~~</th><th>~~4-fold Rate MenACWY, %~~</th><th>~~4-fold Rate MenABCWY, %~~</th><th>~~NI Margin, %~~</th><th>~~Actual Margin, %~~</th><th>~~Power, %~~</th><th>~~n, Group~~</th></tr>
<tr><td>~~A~~</td><td>~~95~~</td><td>~~91~~</td><td>~~−10~~</td><td>~~−4~~</td><td>~~96.00~~</td><td>~~542~~</td></tr>
<tr><td>~~C~~</td><td>~~95~~</td><td>~~93~~</td><td>~~−10~~</td><td>~~−2~~</td><td>~~99.95~~</td><td>~~542~~</td></tr>
<tr><td>~~W~~</td><td>~~95~~</td><td>~~91~~</td><td>~~−10~~</td><td>~~−4~~</td><td>~~96.00~~</td><td>~~542~~</td></tr>
</table></td><td></td></tr>
</table>

~~Y~~	~~95~~	~~93~~	~~−10~~	~~−2~~	~~99.95~~	~~542~~
~~Global~~					~~92.00~~	

~~n = number of participants; NI = Non-inferiority~~
~~For each serogroup: NI limit is −10%~~

Family 1: ~~For the secondary immunogenicity objective, it is assumed~~ Assuming that MenABCWY and MenACWY groups will induce a 4-fold rise in about 95% of the participants for each of the 4 serogroups (Table 15)**, and** ~~U~~**u**sing a 1-sided score test (Miettinen, 1985), non-inferiority margin of −10% and actual margin of 0%, an estimated number of evaluable participants (**n** = 225~~ and 542 for MenABCWY and MenACWY, respectively~~) and individual powers of 99.87% for each A, C, W, and Y serogroup test, will give a global power of 99.48% to demonstrate non-inferiority of MenABCWY versus MenACWY.

Family 2: Assuming that MenACWY group will induce a 4-fold rise in about 95% of the participants for each of the 4 serogroups; MenABCWY will induce a 4-fold rise in about 91% of the participants for A and W serogroups, and 93% of the participants for C and Y serogroups; and, using a 1-sided score test (Miettinen, 1985), non-inferiority margin of −10% and actual margins as given in Table 14, an estimated evaluable participants (n=542) and individual powers of 96.00%, 99.95%, 96.00%, and 99.95% for each A, C, W, and Y serogroup test, will give a global power of 91% to demonstrate NI of MenABCWY versus MenACWY.

~~Table 15 Power to Demonstrate Immunological Non-inferiority for Serogroups A, C, W, and Y of MenABCWY Compared to MenACWY (Secondary)~~

~~Serogroup~~	~~4-fold Rate MenACWY, %~~	~~4-fold Rate MenABCWY, %~~	~~NI Margin, %~~	~~Actual Margin, %~~	~~Power, %~~	~~n, ABCWY/ACWY~~
~~A~~	~~95~~	~~95~~	~~−10~~	~~0~~	~~99.87~~	~~225/542~~
~~C~~	~~95~~	~~95~~	~~−10~~	~~0~~	~~99.87~~	~~225/542~~
~~W~~	~~95~~	~~95~~	~~−10~~	~~0~~	~~99.87~~	~~225/542~~
~~Y~~	~~95~~	~~95~~	~~−10~~	~~0~~	~~99.87~~	~~225/542~~
~~Global~~					~~99.48~~	

~~n = number of participants; NI = Non-inferiority~~
~~For each serogroup: Non-inferiority limit is −10%~~

For the multiplicity adjustment, all hypotheses will be ranked into two families according to the following power of test:

Table 14 Power to Demonstrate Immunological Non-inferiority for Serogroups A, C, W, and Y of MenABCWY Compared to MenACWY (Primary)

Serogroup	4-fold rate MenACWY	4-fold rate MenABCWY	NI margin	Actual margin	Power	N ABCWY/ ACWY
Family 1: NI, 2-sided score test (Miettinen and Nurminen, 1985)						
A	**95%**	**95%**	**-10%**	**0%**	**99.87%**	**225**
C	**95%**	**95%**	**-10%**	**0%**	**99.87%**	**225**
W	**95%**	**95%**	**-10%**	**0%**	**99.87%**	**225**
Y	**95%**	**95%**	**-10%**	**0%**	**99.87%**	**225**
Family 2: NI, 2-sided score test (Miettinen and Nurminen, 1985)						
A	**95%**	**91%**	**-10%**	**-4%**	**96.00%**	**542**
C	**95%**	**93%**	**-10%**	**-2%**	**99.95%**	**542**
W	**95%**	**91%**	**-10%**	**-4%**	**96.00%**	**542**

Section # and Name	Description of Change	Brief Rationale
	Y | **95%** | **93%** | **-10%** | **-2%** | **99.95%** | **542** **Global Power** | **91.00%** **n = number of participants; NI = non-inferiority** ~~Considering that approximately 10% of the selected participants might withdraw or not be evaluable for the immunogenicity objectives, the target sample size to be analyzed is 853 participants (603 and 250 participants for ACWY and ABCWY respectively).~~ **Considering that approximately 10% of the selected participants might withdraw or not be evaluable for the immunogenicity objectives, the target sample size to be analyzed will be 270 participants per group and 603 participants per group for the first co-primary and the second co-primary objectives respectively.** Evaluable means all participants included in the set for the statistical analysis defined in Section 9.3. The sample size calculation was performed in PASS 12 (Hintze, 2013). The global power for all 4 strains **across Family 1 and Family 2** is the product of individual powers.	
9.3 Populations for Analyses	The text in the table was revised as follows: Participant who agreed/participant 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 or received study intervention or undergone an invasive procedure.	
9.4.1 General Considerations	The following bullet point list item was revised as follows *(the added content is bold; the deleted text is crossed out)*: • ~~No multiplicity adjustment is foreseen as NI is considered achieved when the criterion is met for all 4 strains. This is applicable for both primary and secondary NI objectives.~~ **Fixed sequential testing**	

Section # and Name	Description of Change	Brief Rationale
	with full alpha propagation in pre-ordered hypotheses families (Family 1 and Family 2, as defined in Section 9.1) will be applied.	
9.4.3.1 Immunological Non-inferiority of MenABCWY vs. MenACWY	The following text was revised as follows *(the added content is bold; the deleted text is crossed out)*: *Statistical method* ***(Family 1)***: For each of the serogroups A, C, W, and Y, the percentages of participants with 4-fold rise (refer to Section 9.4.1), and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each study group at 1 month after the ~~first~~ second vaccination. The standardized asymptotic CIs between group differences in percentages will be derived using the method of Miettinen and Nurminen (Miettinen, 1985). The following text was added: *Statistical method (Family 2)*: For each of the serogroups A, C, W, and Y, the percentages of participants with 4-fold rise (refer to Section 9.4.1), and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each study group at 1 month after the first vaccination. The standardized asymptotic CIs between group differences in percentages will be derived using the method of Miettinen and Nurminen (Miettinen, 1985). ***NI criterion:*** Non-inferiority will be demonstrated if, the lower limit of 2-sided 95% CI for the percent difference in 4-fold rise in hSBA titers (p1_MenABCWY − p1_MenACWY) is above −10%, for each serogroup A, C, W, and Y.	
9.4.4 Secondary Endpoints	Section 9.4.4.1 “Immunological Non-Inferiority of MenABCWY vs. MenACWY” was deleted with all its content. Numbering of subsequent subsections in Section 9.4.4. shifted accordingly.	

Section # and Name	Description of Change	Brief Rationale
Appendix 1 Abbreviations and Glossary of Terms	New abbreviations added: **ADE** **SADE** **USADE** New terms added: **Combination product** **Medical device deficiency**	New terms added to support changes in the protocol text regarding combination products and device deficiencies.
	The following definitions were removed from the Glossary of Terms: **Adverse event** **Adverse event of special interest**	Removed to avoid redundancy: both terms are defined in Appendix 4.
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations	In the subsection "Informed Consent and Assent Process", the following text was added: Re-consent must be obtained in accordance with local laws and regulations for participants who become legally emancipated during the study, i.e. reach the legal age of consent. The participant can provide consent by signing/witnessing/thumb printing an ICF, similar to that provided to the parent(s)/LAR(s) at study start, which summarizes the study and includes a consent statement and documents that the participant agrees to continue participating in the study.	As an additional consideration for consent process applicable to the study population.
	The subheading "Study and Study Center Start and Closure" was renamed to "Study and Study Center ~~Start and~~ Closure" In the subsection "Study and Study Center Closure", the following text was	For clarity.

Section # and Name	Description of Change	Brief Rationale
	added. An additional item in the list of reasons for study closure: • Total number of participants included earlier than expected An addditional paragraph: If the study is prematurely terminated or suspended, IQVIA shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, for the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.	
Appendix 4 **Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting**	In the section "Potential Immune-Mediated Diseases (pIMDs)", the following text was removed: If pIMDs are the only AESIs collected during the study, this should be explicitly mentioned in this section and the term "AESI" can be replaced by "pIMD" throughout the document. Adapt the following list of pIMDs based on the discussion with the project Safety Physician if more disorders need to be considered.	To correct the error as this text played administrative role and was not part of the content of the section.
	The table heading was revised as follows *(the removed text is crossed out)*: Assessment of Intensity ~~and Toxicity~~	To correct the error, as toxicity assessment methods are not described in the associated table.
	The following information was added *(only the paragraph headers are shown; see the added content in the body of the appendix)*: **Definitions of Medical Device Adverse Events and Adverse Device Effects** **Definitions of a Medical Device SAE, Serious Adverse Device Effect,**	To provide instructions on identifying, recording, and reporting of device-related safety events

Section # and Name	Description of Change	Brief Rationale
	and Unexpected Serious Adverse Device Effect **Recording and Reporting of Medical Device AE, ADEs, SADEs and USADE**	
Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information	In the table "Highly Effective Contraceptive Methods", subheading "Highly Effective Contraceptive Methods That Are User Dependent", the text was updated as follows *(the added text is **bold**)*: Progestogen-only hormonal contraception associated with inhibition of ovulation • **Oral** • Injectable	The oral contraception method was considered acceptable as discussed for V72_72 Phase III study. The oral contraception method will allow enrollment of more potential participants into the study.
	In the table "Highly Effective Contraceptive Methods", subheading "Highly Effective Methods That Are User Independent", the following item was aligned with other items on the list with an added bullet point: • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation	To correct the formatting error that affected accuracy on the content.
Administrative Changes		
Title Page	*Original text:* Amendment Number: Amendment 1 *New Text:* Amendment Number: 2 *Original date:* 31 August 2020 *New date:* 12 February 2021	To reflect the change in the protocol version
Page Headers	*Original text:* Protocol 213171 (MENABCWY-019) – Amendment 2	To reflect the change in the protocol version

Section # and Name	Description of Change	Brief Rationale
	New text: Protocol 213171 (MENABCWY-019) – Amendment 3	
Appendix 7 Protocol Amendment History	The new appendix added to include the summaries of changes from previous protocol amendments, 1 and 2.	To retain the history of previous protocol amendments
Appendix 8 Signature of Investigator	The number of the appendix changed from 7 to 8.	Due to addition of Appendix "Protocol Amendment History"
	Original text: VERSION: Amendment 2 *New text:* VERSION: Amendment 3	To reflect the change in the protocol version
Additional administrative changes	Page numbers, Table of Contents, Table of Tables were updated. Table numbering shifted. Relevant editorial changes were also made (e.g., internal cross-references, formatting).	Updates were made according to the changes in the content of the document

Amendment 1 - 31 August 2020

This amendment was considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacted the safety or physical/mental integrity of subjects nor the scientific value of the study.

Overall Rationale for the Amendment:

This protocol was amended to correct the volume of normal saline which comprised the placebo used in this study.

Description of Changes in Amendment 1:

Section # and Name	Description of Change	Brief Rationale
6.1 Study Interventions Administered	Table 8 was updated to reflect the following changes: Dose form; Placebo: changed from "Suspension for injection" to "Solution for Injection" Vaccines(s)/ Product Formulation; Placebo: Sodium chloride (NaCl) (0.9%) Water for injections was added and NaCl, water for injections q.s. 0.5 ml was deleted Volume to be administered; Placebo: Changed from 0.5mL to 0.65mL Footnote 11 was added: The volume of the saline PFS may be between 0.6 mL and 0.8 mL. The full volume is to be injected	Change in placebo volume from 0.5 mL to 0.65 mL to be aligned with the Certificate of Analysis.

Appendix 8 Signature of Investigator

PROTOCOL TITLE: A phase IIIB, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of GSK's Meningococcal ABCWY vaccine when administered in healthy adolescents and adults, previously primed with MenACWY vaccine

PROTOCOL NO: 213171 (MENABCWY-019)

VERSION: Amendment 3

This protocol is a confidential communication of GlaxoSmithKline Biological SA (GSK). I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from GSK.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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