Protocol Amendment 7

Study ID: 205419

Official Title of Study: Safety and Immunogenicity Study of GSK Meningococcal Group B Vaccine Bexsero (GSK3536829A) when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine Menveo (GSK3536820A) to Healthy Subjects 16-18 Years of Age

NCT number: NCT04318548

Date of Document: 14-Oct-2022

Clinical Study Protocol

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

Primary Study vaccine(s)/product(s) and number(s)	• GlaxoSmithKline (GSK) Biologicals' meningococcal group-B vaccine *Bexsero* (GSK3536829A) • GSK Biologicals' Meningococcal MenACWY Conjugate Vaccine *Menveo* (GSK3536820A)
eTrack study number and abbreviated title	205419 (MENB REC 2ND GEN-045 (V72_79))
Investigational New Drug (IND) number	IND-011561
EudraCT number	2016-003722-16
Date of protocol	Final Version 1: 28 June 2016
Date of protocol amendment	Amendment 1 Final: 14 August 2019 Amendment 2 Final: 23 January 2020 Amendment 3 Final: 29 September 2020 Amendment 4 Final: 26 November 2020 Amendment 5 Final: 13 April 2021 Amendment 6 Final: 21 June 2022 ***Amendment 7 Final: 11 October 2022***
Title	Safety and Immunogenicity Study of GSK Meningococcal Group B Vaccine *Bexsero* (GSK3536829A) when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine *Menveo* (GSK3536820A) to Healthy Subjects 16-18 Years of Age.
Short title	A Phase IIIB, Randomized, Observer-blind, Multicenter Study to Assess the Safety and Immunogenicity of GSK Meningococcal Group B Vaccine when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine to Healthy Subjects 16-18 Years of Age.
Co-ordinating author	PPD Scientific Writing
Contributing authors ***(Amended 11 October 2022)***	• PPD, ***Clinical Sciences Lead*** • PPD Study Delivery Lead • PPD, Local Delivery Lead

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Contributing authors (continued)

(Amended 11 October 2022)

- PPD, Oversight Data Manager
- PPD, Clinical Trials Supply Manager
- PPD Clinical Laboratory Sciences Study Manager
- PPD, Clinical Read-out Team Leader
- PPD PPD
- PPD, ***SERM Principal Scientist***
- PPD Global Regulatory Affairs
- PPD, Study Data Manager
- PPD, Global Patent
- PPD, Study Statistician
- PPD, Lead Statistician
- PPD, PPD, ***Clinical Project Lead*** from Protocol Amendment 3 onwards and PPD, ***Associate Clinical Project Lead*** from Protocol Amendment 6 onwards.

GSK Biologicals' Protocol DS v 16.0

Protocol Amendment 7 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	205419 (MENB REC 2ND GEN-045 (V72_79))
IND number	IND-011561
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Sponsor signatory	Alessandro Ble, ***Director, Associate Clinical Project Lead***
Signature	_____
Date	_____

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

Protocol Amendment 7 Investigator Agreement

I agree:

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

Hence, I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	205419 (MENB REC 2ND GEN-045 (V72_79))
IND number	IND-011561
EudraCT number	2016-003722-16
Date of protocol amendment	***Amendment 7 Final: 11 October 2022***
Title	Safety and Immunogenicity Study of GSK Meningococcal Group B Vaccine *Bexsero* (GSK3536829A) when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine *Menveo* (GSK3536820A) to Healthy Subjects 16-18 Years of Age.
Investigator name	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

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

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

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

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.9.3.

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.4.6.1.

PROTOCOL AMENDMENT 7 SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Protocol Amendment 7	11 October 2022
Protocol Amendment 6	21 June 2022
Protocol Amendment 5	13 April 2021
Protocol Amendment 4	26 November 2020
Protocol Amendment 3	29 September 2020
Protocol Amendment 2	23 January 2020
Protocol Amendment 1	14 August 2019
Original Protocol	28 June 2016

Amendment 7: 11 October 2022

Overall Rationale for the Amendment change

The purpose of the amendment 7 is to shorten the safety follow-up period to 6 months in subjects who have not reached the 6-month safety follow-up after the last dose, at the time this amendment takes effect, as the comprehensive safety data in this population indicates that the safety of the trial participants is not jeopardized and does not pose any meaningful threat. These data include all previous pivotal clinical studies, the recently completed V72_72 study in the same population and post-marketing experience in countries where *Menveo* and *Bexsero* are marketed, and in majority of cases are given concomitantly.

The purpose of this amendment is also to extend the visit window to 28 days post reference day to mitigate the impact of COVID pandemic, including quarantine, mandatory vaccination, or other disturbances in the study procedures.

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

Section # and Name	Description of Change	Brief Rationale
Contributing authors	Updated job titles	Internal update in name of job titles
Sponsor signatory page	Updated job title	Internal update in name of job title
Section 1	Updated objectives and endpoints table Updated overall design figure Updated text	To incorporate 2 additional primary endpoints To incorporate a shortened safety follow-up into the overall design figure To introduce a shortened safety follow-up period in subjects who have not reached safety follow-up (SFU) 5 (Day 271) at the time this amendment takes effect
Table 3	Added a bullet mark for study conclusion also under SFU 5 and added a footnote with details	To introduce a shortened safety follow-up period in subjects who have not reached SFU 5 (Day 271) at the time this amendment takes effect
Table 4	Updated	To extend the visit window to 28 days post reference day
Table 5	Addition of footnote	To introduce a shortened safety follow-up period in subjects who have not reached

Section # and Name	Description of Change	Brief Rationale
		SFU 5 (Day 271) at the time this amendment takes effect
Table 6	Updated	To incorporate 2 additional primary endpoints
Figure 1	Updated	To introduce a shortened safety follow-up period in subjects who have not reached SFU 5 (Day 271) at the time this amendment takes effect
Section 5.2 Section 5.4 Section 7.5.1 Section 8.4.3 Section 8.6 Section 12.5.8	Addition of text	To introduce a shortened safety follow-up period in subjects who have not reached SFU 5 (Day 271) at the time this amendment takes effect
Table 14	Table revised	To provide clarity on what assay to be performed at which visit.
Table 15	Table title edited	To clarify that study conclusion at Day 451 is applicable in subjects who have crossed Day 271
Table 16	New table created	To clarify that study conclusion at Day 271 is applicable in subjects who have not reached Day 271

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1. SYNOPSIS

Indication:

Active immunization against invasive disease caused by *N. meningitidis* serogroup B strains. Although the meningococcal group B vaccine was developed for individuals aged 2 months and older, the actual age range for which this recommendation extends varies depending on the approval from different health authorities. In the US, the current indication is for individuals 10 through 25 years of age.

Rationale:

- Rationale for the study

Data from clinical studies conducted in several age groups show that rMenB+OMV NZ and MenACWY are well tolerated and immunogenic when administered with a number of other vaccine antigens, including Diphtheria, Tetanus and acellular Pertussis (DTPa). Data from an infant study showed that both rMenB+OMV NZ and MenACWY were well tolerated and immunogenic when administered concomitantly in healthy infants. No data is currently available on the concomitant use of rMenB+OMV NZ and MenACWY in adolescents.

The purpose of this clinical study is to evaluate the immunogenicity, the safety, and the tolerability of rMenB+OMV NZ and MenACWY vaccines when concomitantly administered to healthy subjects 16-18 years of age.

- Rationale for the study design

The purpose of this study is to assess the safety and demonstrate the non-inferiority of the antibody responses of rMenB+OMV NZ and MenACWY vaccines when concomitantly administered compared to either alone in healthy subjects 16-18 years of age. The subjects will be randomized to one of the 3 parallel treatment arms in a 1:1:1 ratio to receive the concomitant rMenB+OMV NZ and MenACWY vaccines (Group MenB+MenACWY) or rMenB+OMV NZ vaccine + placebo (Group MenB) or MenACWY vaccine+ placebo (Group MenACWY) in 2 different arms.

- Rationale for the use of placebo

In order to ensure proper blinding, placebo will be administered to subjects in all groups in a staggered fashion. Subjects in Group MenB and Group MenACWY will be administered Placebo at Visit 1 and for subjects in Group MenB+MenACWY, placebo will be administered at Visit 4 (study Day 91).

Objectives and Endpoints *(Amended 11 October 2022)*:

Objectives	Endpoints
Primary	
To assess the safety and tolerability of rMenB+OMV NZ and MenACWY, when administered concomitantly or alone, in healthy subjects 16-18 years of age.	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 30 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, throughout the study period (Day 1/Month 0 to Month ***9***). • The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI throughout the study period (Day 1/Month 0 to Month ***9***). • ***Among subjects who are followed for 12 months after their last dose:*** o ***The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, between SFU 5/Month 9 and SFU 7/Month 15.*** o ***The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI between SFU 5/Month 9 and SFU 7/Month 15.***
To demonstrate the non-inferiority of the antibody response to rMenB+OMV NZ given concomitantly with MenACWY to healthy subjects 16-18 years of age compared to rMenB+OMV NZ administered alone, as measured by serum bactericidal assay using human complement (hSBA) Geometric Mean Titers (GMTs) against *N. meningitidis* serogroup B indicator strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084* (NHBA), at one month after the second vaccination with rMenB+OMV NZ. *Criterion: Non-inferiority will be demonstrated if for each of the four serogroup B test strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus rMenB+OMV NZ alone) is >0.5.*	• Co-primary endpoints for Group MenB+MenACWY and Group MenB are the hSBA GMTs for rMenB+OMV NZ against each of the four serogroup B test strains (M14459, 96217, NZ98/254 and M07-0241084) at one month after the second vaccination with rMenB+OMV NZ (Visit 4, Month 3).

Objectives	Endpoints
To demonstrate the non-inferiority of the antibody response to MenACWY given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone, as measured by hSBA GMTs against each of the *N. meningitidis* serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY. *Criterion: Non-inferiority will be demonstrated if for each of the four serogroups A, C, W and Y, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus MenACWY alone) is >0.5.*	• Co-primary endpoints for Group MenB+MenACWY and Group MenACWY are the hSBA GMTs against each of the four serogroups A, C, W and Y with MenACWY at one month after the study vaccination of MenACWY (Visit 2, Month 1).
Secondary	
To assess the non-inferiority of the responses to MenACWY when given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone as measured by Enzyme-Linked Immunosorbent Assay (ELISA) Geometric Mean Concentrations (GMCs) against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY. *Criterion: Non-inferiority will be demonstrated if for each of the four A, C, W and Y strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of ELISA GMCs (MenACWY with rMenB+OMV NZ versus MenACWY alone) is >0.5.*	**Immune response to MenACWY** The immune response to MenACWY when administered with/without rMenB+OMV NZ at one month after the first vaccination (Visit 2, Month 1; Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as ELISA GMCs.
To assess the immune response to rMenB+OMV NZ in healthy subjects 16-18 years of age against *N. meningitidis* serogroup B test strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084* (NHBA), at one month after the first and the second vaccination with rMenB+OMV NZ.	**Immune response to rMenB+OMV NZ** The immune response to rMenB+OMV NZ when administered with/without MenACWY will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B test strains M14459, 96217, NZ98/254 and M07-0241084 in both MenB+MenACWY and MenB Groups as following: • GMTs at one month after first and second vaccination with rMenB+OMV NZ and Geometric Mean Ratio (GMRs) at one month after the first (Visit 2, Month 1) and the second (Visit 4, Month 3) rMenB+OMV NZ vaccination compared to the baseline at Visit 1, Day 1/Month 0. • The percentage of subjects with hSBA titers ≥ Lower Limit of Quantitation (LLOQ) for each and all serogroup B test strains, one month after the first (Visit 2, Month 1) and second (Visit 4, Month 3) vaccination. • The percentage of subjects with fourfold increase in hSBA titers relative to baseline (Visit 1, Day 1/Month 0) is defined as: – For a pre-vaccination titer < limit of detection (LOD), a post-vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater, – For a pre-vaccination titer ≥LOD but <LLOQ, a post vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the LLOQ,

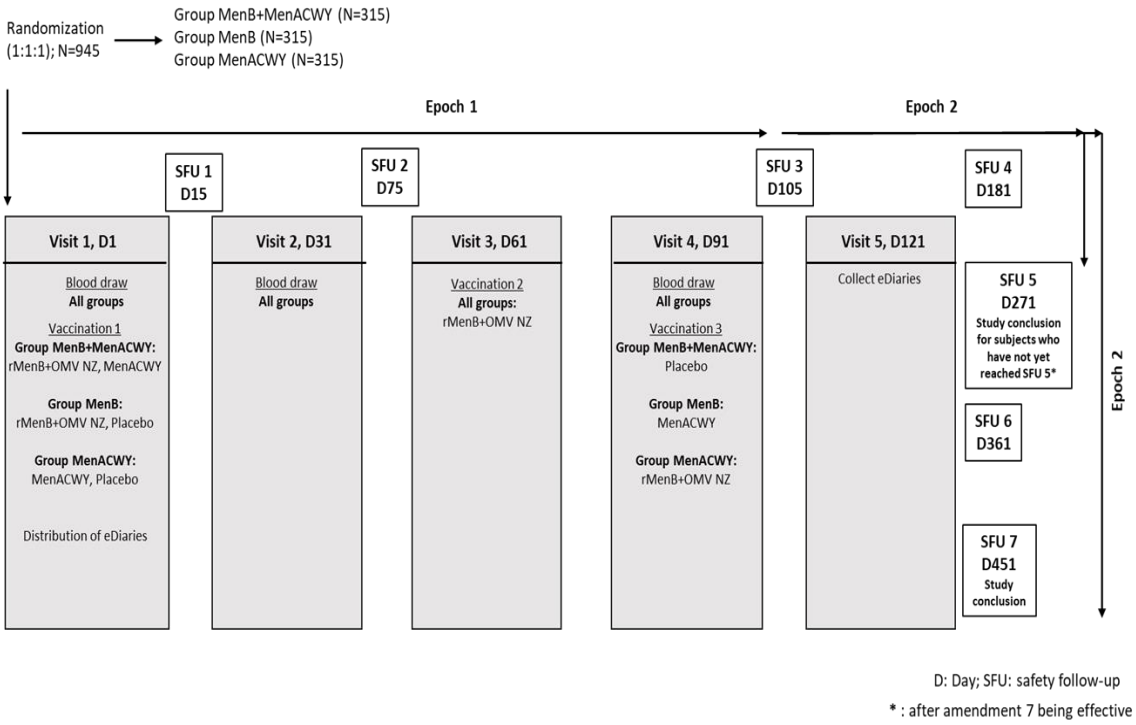
Objectives	Endpoints
	– For a pre-vaccination titer ≥ LLOQ, a post vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the pre-vaccination titer (for Groups MenB+MenACWY and MenB). • The ratio of GMTs (rMenB+OMV NZ when administered with MenACWY [Group MenB+MenACWY] versus rMenB+OMV NZ when administered alone [Group MenB]), one month after the first vaccination (Visit 2, Month 1).
To assess the immune response to MenACWY in healthy subjects 16-18 years of age against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY.	**Immune response to MenACWY** The immune response to MenACWY when administered with/without rMenB+OMV NZ at baseline (i.e. pre-vaccination, Visit 1, Day 1/Month 0) and at one month after the first vaccination (Visit 2, Month 1; Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as: • The percentage of subjects with hSBA titers ≥LLOQ, for each serogroup. • GMRs at one month after first vaccination compared to baseline • The percentage of subjects with fourfold increase in hSBA titers relative to baseline (Visit 1, Day 1/Month 0) is defined as: – For a pre-vaccination titer < LOD, a post-vaccination titer (Visit 2, Month 1) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater, – For a pre-vaccination titer ≥LOD but <LLOQ, a post vaccination titer (Visit 2, Month 1) of at least fourfold the LLOQ, – For a pre-vaccination titer ≥ LLOQ, a post vaccination titer (Visit 2, Month 1) of at least fourfold the pre-vaccination titer (for Groups MenB+MenACWY and MenACWY).
CCI [redacted]	

*The NHBA indicator strain M07-0241084 may be subject to change during the study before clinical testing starts. In this case, this change will be documented in the clinical report.

The study will be deemed successful if both:

1. the non-inferiority of rMenB+OMV NZ when given concomitantly with MenACWY versus rMenB+OMV NZ alone and
2. the non-inferiority of MenACWY when given concomitantly with rMenB+OMV NZ versus MenACWY alone are demonstrated.

Overall Design *(Amended 11 October 2022)*:



Approximately 945 subjects will be screened to achieve 750 evaluable subjects for an estimated total of 250 evaluable subjects per treatment group. Withdrawals will not be replaced.

- Experimental design: Phase IIIB, observer-blind, randomized, controlled, multi-centric, study with 3 parallel groups.
- Study groups:
  - Group MenB+MenACWY: rMenB+OMV NZ given concomitantly with MenACWY at study Day 1; rMenB+OMV NZ at study Day 61; Placebo at study Day 91.
  - Group MenB: rMenB+OMV NZ given concomitantly with Placebo at study Day 1 and rMenB+OMV NZ at study Day 61; MenACWY at study Day 91.
  - Group MenACWY: MenACWY given concomitantly with Placebo at study Day 1; rMenB+OMV NZ at study Day 61 and at study Day 91.
- Duration of the study:
  - Epoch 001: Primary starting at Visit 1 (Day 1) and ending at Visit 4 (Day 91)
  - Epoch 002: Safety follow-up period starting at Visit 4 (Day 91) and ending at Study termination-call (Day 451 [Month 15]) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 at the time this amendment takes effect***

2. SCHEDULE OF ACTIVITIES (SOA)

Table 3 Schedule of Activities *(Amended 11 October 2022)*

Age (years)	16-18 at study start												Notes
Epoch	*Epoch 001*						*Epoch 002*						
Type of contact¥	Visit 1	SFU 1	Visit 2	Visit 3	SFU 2	Visit 4	SFU 3	Visit 5	SFU 4	SFU 5¥	SFU 6	SFU 7	
Timepoint (s) [refer to Table 4 and Table 5 for visit windows]	Day 1	Day 15	Day 31	Day 61	Day 75	Day 91	Day 105	Day 121	Day 181	Day 271	Day 361	Day 451	
Sampling timepoints	Pre-Vacc I		Post-Vacc I			Pre-Vacc III							
Informed consent	●												Activities that can be performed at a separate visit before Visit 1 (approximately 2 weeks before the Visit 1). AEs / SAEs related to study participation or to a concurrent GSK medication/vaccine should also be recorded starting from this separate visit. Inclusion/exclusion criteria should be re-checked prior to vaccination at visit 1. See Section 12.4.3 for details.
Check inclusion/exclusion criteria	●			●		●							See Section 6.1 and 6.2 for Inclusion and Exclusion criteria.
Collect demographic data	●												See Section 8.2.2 for more information.
Medical history	●												See Section 8.2.3 for more information.
Medical history-directed Physical examination	O												See Section 8.2.3 and 8.2.4 for more information.
Symptom-directed physical examination				O		O							See Section 8.2.4 for more information.
Urine pregnancy test (pre-vaccination)	●			●		●							Only for women of childbearing potential. A pregnancy test is mandatory on Visit 1, Visit 3, and Visit 4 even if performed during a prior separate visit See Section 8.2.5 for more information.

Age (years)	**16-18 at study start**												**Notes**
Epoch	***Epoch 001***						***Epoch 002***						
Type of contact¥	**Visit 1**	**SFU 1**	**Visit 2**	**Visit 3**	**SFU 2**	**Visit 4**	**SFU 3**	**Visit 5**	**SFU 4**	**SFU 5¥**	**SFU 6**	**SFU 7**	
Timepoint (s) [refer to Table 4 and Table 5 for visit windows]	**Day 1**	**Day 15**	**Day 31**	**Day 61**	**Day 75**	**Day 91**	**Day 105**	**Day 121**	**Day 181**	**Day 271**	**Day 361**	**Day 451**	
Sampling timepoints	**Pre-Vacc I**		**Post-Vacc I**			**Pre-Vacc III**							
Check contraindications and warnings and precautions to vaccination	●			●		●							See Section 7.7 and 7.8 for more information.
Pre-vaccination body temperature	●			●		●							See Section 8.2.6 for more information.
Vaccines													
Study group and treatment number allocation	O												See Section 7.2.2.2.1 for more information.
Treatment number allocation for subsequent doses				O		O							See Section 7.2.2.2.2 for more information.
Recording of administered treatment number	●			●		●							See Section 7.2.2 for more information.
Vaccines administration	●			●		●							See Section 7.1 for more information.
Laboratory Assays													
Blood sampling for antibody determination (~20 mL, at each visit)	●		●			●							Blood sample collection on Visit 1 and Visit 4 will be performed before vaccine administration. See Section 8.3.4.1 for more information.
Safety assessments													
Record any concomitant medications/vaccinations¥	●	●	●	●	●	●	●	●	●	●	●	●	See Section 7.5 for more information.
Record any intercurrent medical conditions¥	●	●	●	●	●	●	●	●	●	●	●	●	See Section 7.6 for more information.
Distribution of eDiary	O												
Review of eDiary			O			O		O					

Age (years)	**16-18 at study start**												**Notes**
Epoch	***Epoch 001***						***Epoch 002***						
Type of contact¥	**Visit 1**	**SFU 1**	**Visit 2**	**Visit 3**	**SFU 2**	**Visit 4**	**SFU 3**	**Visit 5**	**SFU 4**	**SFU 5¥**	**SFU 6**	**SFU 7**	
Timepoint (s) [refer to Table 4 and Table 5 for visit windows]	**Day 1**	**Day 15**	**Day 31**	**Day 61**	**Day 75**	**Day 91**	**Day 105**	**Day 121**	**Day 181**	**Day 271**	**Day 361**	**Day 451**	
Sampling timepoints	**Pre-Vacc I**		**Post-Vacc I**			**Pre-Vacc III**							
Return of eDiary								O					
30 minutes post-injection assessment	●			●		●							
Recording of solicited adverse events (Days 1–7 post vaccination) in eDiary	O			O		O							
Recording of unsolicited adverse events within 30 days post-vaccination	●	●	●	●	●	●	●	●					
Recording of unsolicited AEs leading to vaccine/study withdrawal, medically attended AEs, SAEs, pregnancies and AESIs***¥**	●	●	●	●	●	●	●	●	●	●	●	●	See Section 12.5.8 for more information.
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine****¥**	●	●	●	●	●	●	●	●	●	●	●	●	
Study Conclusion**¥**										●		●	See Section 5.4 for more information.

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
*COVID-19 infection-related AEs and SAEs should also be recorded on a separate eCRF page.
**Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a parent(s)/LAR(s) or participant signs the consent form to the end of the study
¥ Safety follow up and contact will terminate at SFU 5 for subjects who have not reached SFU 5 at the time this amendment takes effect. Please note that for these subjects, the termination call would be performed at SFU 5.

Whenever possible, the investigator should arrange study visits within the intervals described in Table 4. For safety follow-up calls, the windows in Table 5 will apply.

Table 4 Intervals between study visits *(Amended 11 October 2022)*

Interval	Length of interval	Allowed interval
Visit 1 → Visit 2	30 days	23 - ***58*** days
Visit 1 → Visit 3	60 days	53 - ***88*** days
Visit 3 → Visit 4	30 days	23 - ***58*** days
Visit 4 → Visit 5	30 days	23 - ***58*** days

Table 5 Intervals between study visits and safety follow-up calls *(Amended 11 October 2022)*

Interval	Length of interval	Allowed interval
Visit 1 → SFU 1	14 days	11 - 17 days
Visit 3 → SFU 2	14 days	11 - 17 days
Visit 4 → SFU 3	14 days	11 - 17 days
Visit 4 → SFU 4	90 days	83 - 111 days
Visit 4 → SFU 5*	180 days	173 - 201 days
Visit 4 → SFU 6	270 days	263 - 291 days
Visit 4 → SFU 7	360 days	353 – 381 days

Safety follow up will terminate at SFU 5 for subjects who have not reached SFU 5 at the time this amendment takes effect.

3. INTRODUCTION

3.1. Study rationale

Data from clinical studies conducted in several age groups show that rMenB+OMV NZ and MenACWY are well tolerated and immunogenic when administered with a number of other vaccine antigens, including DTPa. Data from an infant study showed that both rMenB+OMV NZ and MenACWY were well tolerated and immunogenic when administered concomitantly in healthy infants (aged 3 to 13 months). No data is currently available on the concomitant use of rMenB+OMV NZ and MenACWY in adolescents.

The purpose of this clinical study is to evaluate the immunogenicity, the safety and the tolerability of rMenB+OMV NZ and MenACWY vaccines when concomitantly administered to healthy subjects 16-18 years of age.

3.2. Background

Invasive meningococcal disease (IMD) occurs when the normally asymptomatically carried bacterium *Neisseria meningitidis* (*N. meningitidis)* enters the bloodstream, multiplies and causes sepsis. If the bacteria cross the blood–brain barrier, meningitis occurs [Khatami, 2010].

IMD occurs worldwide. Although incidence varies in different regions of the world, infants, children and adolescents are the most vulnerable to developing invasive disease. Symptoms of the disease occur rapidly and often result in severe outcomes within a few

hours; otherwise, healthy individuals can be permanently disabled or disfigured or die of the disease. Despite the availability of medical treatment and effective antibiotics for IMD, approximately 9% of European patients die, with case-fatality rates generally increasing with age [ECDC, 2016]. In the US, the overall case-fatality ratio remains at 10%–15%, and 11%–19% of survivors have long-term sequelae [Cohn, 2013].

No reliable estimates of the global burden of disease are currently available as case definitions differ and surveillance data from many regions are incomplete [WHO, 2011]. The overall incidence of confirmed IMDs in European countries in 2012 ranged from 0.11 to 1.77 cases per 100,000 populations [ECDC, 2016]. In the US, the incidence was 0.18 cases per 100,000 population in 2014 [Adams, 2016].

Currently, 13 serogroups of pathogenic *N. meningitidis* [Harrison, 2013] are known to exist; however, virtually all meningococcal meningitis and septicemia are caused by only six serogroups: (i.e., A, B, C, W, Y and X). The introduction of conjugate serogroup C meningococcal vaccines has dramatically changed the epidemiology of disease in industrialized nations, showing potential for broader control with A, C, W and Y conjugates, and leaving serogroup B as the predominant cause of disease. Development of vaccines for prevention of serogroup B disease in industrialized nations and serogroup A conjugate vaccines for Africa could lead to global control of meningococcal disease [Khatami, 2010].

For the US, the 2015 Centers for Disease Control (CDC) data indicate a total of 370 cases and 60 deaths attributable to meningococcal disease, with the majority of these caused by serogroup B, C and Y infections [Cohn, 2013; CDC, 2015]. In Europe, the incidence of disease due to serogroup B is particularly high in Ireland, the United Kingdom, Denmark, and Spain. These same countries had early introduction of Meningococcal serogroup C vaccination after high incidences of serogroup C infections in the late 1990s [ECDC, 2016].

In Europe, the majority of disease occurs in infants under 1 year of age, followed by children from 1 to 5 years of life. A second peak occurs in adolescents 15 to 19 years of age. In the US, incidence of meningococcal disease peaks in 3 age groups: infants and children aged <5 years, adolescents and young adults aged 16 through 21 years, and adults aged ≥65 years. Approximately 60% of disease in the first year of life is caused by serogroup B [Cohn, 2013].

Capsular polysaccharide vaccines have been used successfully in preventing disease and limiting epidemics and outbreaks caused by meningococcal serogroups A, C, W and Y.

However, the capsular polysaccharide of serogroup B is poorly immunogenic in humans, possibly due to antigenic similarities in serogroup B carbohydrate moieties to carbohydrates widely distributed in the human body. As a result, research has focused on proteins in the outer membrane of meningococci as potential antigens for candidate vaccines. Serogroup B vaccines based on protein-containing outer membrane vesicles (OMV) have been safe and effective in controlling epidemic disease caused by strains homologous to the vaccine strain in Cuba, Brazil, Chile, Norway, and New Zealand. The use of these OMV vaccines to combat serogroup B meningococcal disease has been

limited; however due to the strain-specific nature of the protection and the lack of consistent efficacy in young children.

The knowledge gained during vaccine development for the Norwegian (MenBvac) and New Zealand (MeNZB) epidemics, together with the identification of the *N. meningitidis* serogroup B genome sequence, was used to develop GSK's serogroup B meningococcal vaccine (rMenB+OMV NZ). The availability of the bacterial genome sequence allowed identification of conserved surface-exposed outer membrane proteins of serogroup B strains that were targets for bactericidal antibodies [Pizza, 2000].

On 23 January 2015, the US Food and Drug Administration approved a biologics licence application for GSK meningococcal group B vaccine according to the regulations for accelerated approval; the vaccine was approved for use in individuals 10 through 25 years of age.

Data from clinical studies conducted in several age groups show that both rMenB+OMV NZ and MenACWY are well tolerated and immunogenic when administered with a number of other vaccine antigens, including DTPa. Data from an infant study showed that both rMenB+OMV NZ and MenACWY were well tolerated and immunogenic when administered concomitantly in healthy infants [Clinicaltrials.gov]. However, no data is currently available on the concomitant use of rMenB+OMV NZ and MenACWY in adolescents.

Please refer to the current Investigator Brochure (IB) for information regarding the pre-clinical and clinical studies and the epidemiological information of *Bexsero* (rMenB+OMV NZ).

3.3. Benefit/Risk assessment

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

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

3.3.1. Risk assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational vaccine: rMenB+OMV NZ (*Bexsero*)		
Important potential risk: **Guillain-Barre Syndrome (GBS)**	GBS has been observed with other vaccines. No cases have been identified in the *Bexsero* clinical development program.	The potential risk of events of possible autoimmune aetiology that might occur is mentioned in the Informed Consent Form (ICF). GBS will be monitored through the potential immune-mediated diseases (pIMDs) and SAE collection (see Section 12.5.5.2).
Important potential risk: **Acute disseminated encephalomyelitis (ADEM)**	ADEM has been observed with other vaccines. No cases have been reported during the *Bexsero* clinical development program.	The potential risk of events of possible autoimmune aetiology that can occur is mentioned in the ICF. ADEM will be monitored through the pIMD and SAE collection (see Section 12.5.5.2).
Important potential risk: **Anaphylaxis and anaphylactic shock**	No cases of anaphylaxis to be related to *Bexsero* have been reported in the *Bexsero* clinical development program. However, one case of anaphylaxis within 30 minutes following vaccination was reported in a third party expanded access program (V72_70TP). Allergic reaction (including anaphylactic reaction) is listed in the *Bexsero* US PI.	Anaphylaxis following the administration of *Bexsero* constitutes a contraindication (see section 7.7). Subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis (see Section 8.2.1). Hypersensitivity, including allergy to any component of vaccines, are exclusion criteria in this study (see Section 6.2).
Important potential risk: **Arthritis**	This potential risk is based on a signal observed for *Bexsero*. Attenuated live virus vaccines (rubella) were reported to be associated with joint-related diseases [Tingle, 1986]. Among inactivated vaccines, different manifestations of arthritis following hepatitis B vaccination (psoriatic arthritis, reactive arthritis, etc.) were described [IOM, 2011]. However, no association with meningococcal vaccines has been reported in the literature. One clinical case of juvenile idiopathic arthritis (JIA) possibly related to *Bexsero* and 6 spontaneous reports considered to have a possible causal relationship have been observed.	Arthritis will be monitored through the AESI collection (see Section 12.5.5.1).

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational vaccine: MenACWY (*Menveo*)		
Important Identified risk: **Reconstitution errors**	Cases describing medication errors due to administration of the MenCWY conjugate liquid component only without reconstitution with the MenA conjugate lyophilized component, or due to administration of the MenA conjugate lyophilized component only after reconstitution with a different solvent, have been reported during the MenACWY clinical development program.	In several sections of the protocol (e.g., Section 7.1. "Description of study vaccines") it is clarified that the 2 vaccine components have to be reconstituted before vaccine injection.
Important potential risk: **GBS**	GBS has been observed with other vaccines. No cases have been reported during the MenACWY clinical development program.	The potential risk of events of possible autoimmune aetiology that might occur is mentioned in ICF. GBS will be monitored through the pIMDs and SAE collection (see Section 12.5.5.2).
Important potential risk: **ADEM**	ADEM has been observed with other vaccines. Two serious cases from clinical trials were retrieved from the GSK's global safety database for MenACWY. None of them has provided sufficient evidence of a causal association between ADEM and MenACWY.	The potential risk of events of possible autoimmune aetiology that can occur is mentioned in the ICF. ADEM will be monitored through the pIMD and SAE collection (see Section 12.5.5.2).
Important potential risk: **Thrombocytopenia**	Immune thrombocytopenic purpura has been reported in association with several licensed vaccines. One serious case related to MenACWY has been reported during the clinical development program. This case didn't provide sufficient evidence of a causal association between thrombocytopenia and MenACWY vaccine.	Immune thrombocytopenic purpura will be monitored through SAE collection (see Section 12.5.5.2).
Important potential risk: **Facial paresis**	Facial paresis was recognized as an important potential risk following the results of a sponsored observational study (V59_34OB) which found an imbalance of cases of facial paresis following vaccination with MenACWY, mainly when administered concomitantly with other vaccines. No cases of facial paresis were reported from interventional clinical trials.	Paralysis of the face is mentioned in the list of side effects in the ICF. Facial paresis will be monitored through SAE collection.
Study Procedures		
Risk of blood sampling	Blood sampling is associated with a risk of syncope, dizziness, and infection after or during venipuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the health of the subject.

3.3.2. Benefit assessment

- Receiving GSK's meningococcal vaccines *Bexsero* and *Menveo* during the study duration may protect against meningococcal IMDs caused by *N. meningitidis* serogroups A, B, C, W, Y.
- Medical monitoring and evaluations/assessments associated with this study.

3.3.3. Overall Benefit: Risk conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential or identified risks identified in association with rMenB+OMV NZ and MenACWY are justified by the potential benefits (prevention) that may be afforded to subjects receiving rMenB+OMV NZ and MenACWY.

4. OBJECTIVE(S) AND ENDPOINT(S)

Table 6 Study objectives and endpoints *(Amended 11 October 2022)*

Objectives	Endpoints
Primary	
To assess the safety and tolerability of rMenB+OMV NZ and MenACWY, when administered concomitantly or alone, in healthy subjects 16-18 years of age.	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 30 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, throughout the study period (Day 1/Month 0 to Month ***9***). • The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI throughout the study period (Day 1/Month 0 to Month ***9***). • ***Among subjects who are followed for 12 months after their last dose:*** o ***The frequencies and percentages of subjects with***

Objectives	Endpoints
	SAEs, AEs leading to withdrawal, between SFU 5 (Month 9) and SFU 7 (Month 15). The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI between SFU 5 (Month 9) and SFU 7 (Month 15).
To demonstrate the non-inferiority of the antibody response to rMenB+OMV NZ given concomitantly with MenACWY to healthy subjects 16-18 years of age compared to rMenB+OMV NZ administered alone, as measured by serum bactericidal assay using human complement (hSBA) Geometric Mean Titers (GMTs) against *N. meningitidis* serogroup B indicator strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084* (NHBA), at one month after the second vaccination with rMenB+OMV NZ. *Criterion: Non-inferiority will be demonstrated if for each of the four serogroup B test strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus rMenB+OMV NZ alone) is >0.5.*	Co-primary endpoints for Group MenB+MenACWY and Group MenB are the hSBA GMTs for rMenB+OMV NZ against each of the four serogroup B test strains (M14459, 96217, NZ98/254 and M07-0241084) at one month after the second vaccination with rMenB+OMV NZ (Visit 4, Month 3).
To demonstrate the non-inferiority of the antibody response to MenACWY given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone, as measured by hSBA GMTs against each of the *N. meningitidis* serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY. *Criterion: Non-inferiority will be demonstrated if for each of the four serogroups A, C, W and Y, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus MenACWY alone) is >0.5.*	Co-primary endpoints for Group MenB+MenACWY and Group MenACWY are the hSBA GMTs against each of the four serogroups A, C, W and Y with MenACWY at one month after the study vaccination of MenACWY (Visit 2, Month 1).
Secondary	
To assess the non-inferiority of the responses to MenACWY when given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone as measured by Enzyme-Linked Immunosorbent Assay (ELISA) Geometric Mean Concentration (GMCs) against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY. *Criterion: Non-inferiority will be demonstrated if for each of the four A, C, W and Y strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of ELISA GMCs (MenACWY with rMenB+OMV NZ versus MenACWY alone) is >0.5.*	**Immune response to MenACWY** The immune response to MenACWY when administered with/without rMenB+OMV NZ one month after the first vaccination (Visit 2, Month 1, Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as ELISA GMCs.
To assess the immune response to rMenB+OMV NZ in healthy subjects 16-18 years of age against *N. meningitidis* serogroup B test strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084 (NHBA), at one month after the first and the second vaccination with rMenB+OMV NZ.	**Immune response to rMenB+OMV NZ** The immune response to rMenB+OMV NZ when administered with/without MenACWY will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B test strains M14459, 96217, NZ98/254 and M07-0241084 in both MenB+MenACWY and MenB Groups as following:

Objectives	Endpoints
	• GMTs at one month after first (Visit 2, Month 1) and second (Visit 4, Month 3) vaccination with rMenB+OMV NZ and Geometric Mean Ratio (GMRs) at one month after the first and the second rMenB+OMV NZ vaccination compared to the baseline at Visit 1, Day 1/Month 0. • The percentage of subjects with hSBA titers ≥ Lower Limit of Quantitation (LLOQ) for each and all serogroup B test strains, one month after the first (Visit 2, Month 1) and second (Visit 4, Month 3) vaccination. • The percentage of subjects with fourfold increase in hSBA titers relative to baseline (Visit 1, Day 1/Month 0) defined as: – For a pre-vaccination titer < limit of detection (LOD), a post-vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater, – For a pre-vaccination titer ≥LOD but <LLOQ, a post vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the LLOQ, – For a pre-vaccination titer ≥ LLOQ, a post vaccination titer (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the pre-vaccination titer (for Groups MenB+MenACWY and MenB). • The ratio of GMTs (rMenB+OMV NZ when administered with MenACWY [Group MenB+MenACWY] versus rMenB+OMV NZ when administered alone [Group MenB]), one month after the first vaccination (Visit 2, Month 1).
To assess the immune response to MenACWY in healthy subjects 16-18 years of age against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY.	**Immune response to MenACWY** The immune response to MenACWY when administered with/without rMenB+OMV NZ at baseline (i.e. pre-vaccination, Visit 1, Day 1/Month 0) and at one month after the first vaccination (Visit 2, Month 1; Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as: • The percentage of subjects with hSBA titers ≥LLOQ, for each serogroup. • GMRs at one month after first vaccination compared to baseline • The percentage of subjects with fourfold increase in hSBA titers relative to baseline (Visit 1, Day 1/Month 0) is defined as: – For a pre-vaccination titer < LOD, a post-vaccination titer (Visit 2, Month 1) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater,

Objectives	Endpoints
	– For a pre-vaccination titer ≥LOD but <LLOQ, a post vaccination titer (Visit 2, Month 1) of at least fourfold the LLOQ, – For a pre-vaccination titer ≥ LLOQ, a post vaccination titer (Visit 2, Month 1) of at least fourfold the pre-vaccination titer (for Groups MenB+MenACWY and MenACWY).
CCI [redacted]	

*The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

The study will be deemed successful if both:

1. the non-inferiority of the antibody response to rMenB+OMV NZ when given concomitantly with MenACWY versus rMenB+OMV NZ alone and
2. the non-inferiority of the antibody response to MenACWY when given concomitantly with rMenB+OMV NZ versus MenACWY alone are demonstrated.

5. STUDY DESIGN

5.1. Scientific rationale for study design

The purpose of this study is to demonstrate the non-inferiority of the antibody response in terms of Human Serum Bactericidal Assay (hSBA) using human complement GMTs against *N. meningitidis* test strains indicative of serogroups A, C, W, Y, and B, after concomitant rMenB+OMV NZ and MenACWY vaccine administration to either vaccine alone in healthy subjects 16-18 years of age.

The selection of the study population is based on ACIP recommendations for use of meningococcal vaccines [ACIP, 2011]. Routine administration of a MenACWY vaccine for all persons aged 11 through 18 years is recommended. A single dose of vaccine should be administered at 11 or 12 years of age, and a booster dose should be administered at 16 years of age. Adolescents who receive their first dose at 13 through 15 years of age should receive a booster dose at 16 through 18 years of age. In Europe, *Menveo* has been approved by EMA for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to N. *meningitidis* groups A, C, W and Y,

to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations.

To be eligible for this study design, all subjects must have received a previous vaccination with a quadrivalent meningococcal conjugate vaccine (MenACWY; *Menveo* or *Menactra*) at least 4 years prior to study start**.** The available data support interchangeability of the 2 licensed meningococcal conjugate vaccines [ACIP, 2013]. Consequently, a booster dose of *Menveo* can be administered, regardless of the vaccine brand used for the previous dose**.**

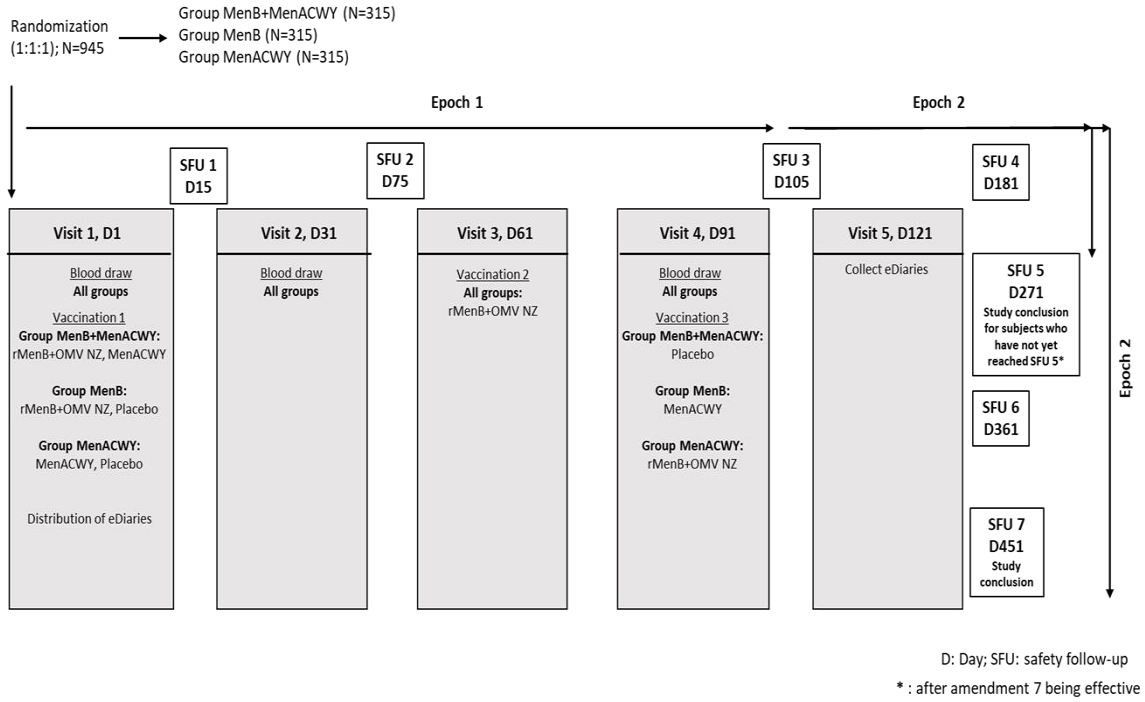
Data collected from this study may support the concomitant use of rMenB+OMV NZ and MenACWY in healthy subjects 16-18 years of age.

5.1.1. Rationale for the use of placebo

In order to ensure proper blinding and uniformity, placebo will be administered at Visit 1 (study Day 1) to subjects in Groups MenB and MenACWY. In addition, at Visit 4 (study Day 91), placebo will be administered to subjects in Group MenB+MenACWY while subjects in Groups MenB and MenACWY will receive MenACWY and rMenB+OMV NZ respectively.

5.2. Overall design *(Amended 11 October 2022)*

Figure 1 Study design overview *(Amended 11 October 2022)*



Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Section 2), are essential and

required for study conduct.

- Type of study: self-contained
- Experimental design: Phase IIIB, observer-blind, randomized, controlled, multi-centric, study with 3 parallel groups.
- Duration of the study:
  - Epoch 001: Primary starting at Visit 1 (Day 1) and ending at Visit 4 (Day 91)
  - Epoch 002: Safety follow-up period starting at Visit 4 (Day 91) and ending at Study termination-call (Day 451 [Month 15]) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 at the time this amendment takes effect.***
  - Primary completion Date (PCD): Study termination-call (Day 451) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 at the time this amendment takes effect.***

Refer to section 12.1.2 for the definition of PCD.

  - End of Study (EoS): Last subject last visit (LSLV) [last concluding contact on Day 451 ***(Month 15) or Day 271 (Month 9) for subjects who have not reached Day 271 at the time this amendment takes effect*** or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

Refer to section 12.1.2 for the definition of EoS.

- Study groups:
  - Group MenB+MenACWY: rMenB+OMV NZ given concomitantly with MenACWY at study Day 1; rMenB+OMV NZ at study Day 61; Placebo at study Day 91.
  - Group MenB: rMenB+OMV NZ given concomitantly with Placebo at study Day 1 and rMenB+OMV NZ at study Day 61; MenACWY at study Day 91.
  - Group MenACWY: MenACWY given concomitantly with Placebo at study Day 1; rMenB+OMV NZ at study Day 61 and at study Day 91.

Table 7 Study groups, treatment and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Vaccine/Product name	Epochs (Blinding)	
					Epoch 001 (observer-blind)	Epoch 002 (observer-blind)
MenB+MenACWY	315	16 years – 18 years	*Bexsero*	rMenB+OMV NZ	x	x
			Menveo	MenACWY (MenA lyo+MenCWY liquid		
			Placebo	*NaCl*		
MenB	315	16 years – 18 years	*Bexsero*	rMenB+OMV NZ	x	x
			Menveo	MenACWY (MenA lyo+MenCWY liquid		
			Placebo	*NaCl*		
MenACWY	315	16 years – 18 years	*Bexsero*	rMenB+OMV NZ	x	x
			Menveo	MenACWY (MenA lyo+MenCWY liquid		
			Placebo	*NaCl*		

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

Visits Study Day	Visit 1 Day 1	Visit 2 Day 31	Visit 3 Day 61	Visit 4 Day 91
Group MenB+MenACWY N=315	Blood Draw rMenB+OMV NZ MenACWY	Blood Draw	rMenB+OMV NZ	Blood Draw Placebo
Group MenB N=315	Blood Draw rMenB+OMV NZ Placebo			Blood Draw MenACWY
Group MenACWY N=315	Blood Draw MenACWY Placebo			Blood Draw rMenB+OMV NZ

- Control: active control.
- Vaccination schedules: Day 1 (Visit 1), Day 61 (Visit 3) and Day 91 (Visit 4)
- Treatment allocation: Subjects to be randomized in a 1:1:1 ratio at Visit 1 (Day 1) to Groups MenB+MenACWY, MenB and MenACWY.
- Blinding: observer-blind.
- Sampling schedule:
  - Blood sampling: For all the 3 groups (i.e., Group MenB+MenACWY, Group MenB, and Group MenACWY), approximately 20 mL sample of blood will be drawn at Visit 1 (Day 1) before the first vaccination, at Visit 2 (Day 31) and at Visit 4 before vaccination (Day 91).
  - Urine sampling: Urine samples for pregnancy testing will be collected from female subjects at Visit 1, Visit 3 and Visit 4 prior to the vaccinations.
- Data collection: Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject Diary (electronic Diary [eDiary]).

5.3. Number of subjects

A maximum of 945 subjects will be randomized such that approximately 750 evaluable subjects complete the study.

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

Withdrawals will not be replaced.

5.4. Subject and study completion

A subject is considered to have completed the study if he/she is available for the concluding contact (Day ***271/***451 safety follow-up contact) as described in the protocol.

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

6. STUDY POPULATION

6.1. Inclusion criteria for enrolment

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

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits) or/and subjects' parent(s)/Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Previous vaccination with one dose of quadrivalent meningococcal conjugate vaccine (MenACWY*, Menveo or Menactra*) at least 4 years prior to informed consent and assent as applicable (according to the subject's age).
- Written or /witnessed/thumb printed informed consent obtained from the subject/parent(s)/LAR(s) of the subject prior to performance of any study specific procedure.
- Written informed assent obtained from the subject (if applicable) along with informed consent from the subject's parent(s)/LAR(s) prior to performing any study specific procedure.
- A male or female between, and including, 16 and 18 years of age at the time of the first vaccination.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause (please refer to Section 12.6.1 for definitions of menarche and menopause).
- Female subjects of childbearing potential may be enrolled in the study, if the subject (refer to Section 12.6.1 for definitions of woman of childbearing potential and adequate contraception):
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination, and
  - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Prior to receipt of second and third study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects do not meet any of the original inclusion criteria listed above, they should not receive additional vaccinations.

6.2. Exclusion criteria for enrolment

6.2.1. Medical conditions

- Progressive, unstable, or uncontrolled clinical conditions.
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
- Abnormal function of the immune system resulting from:
  - Clinical conditions.
  - Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to study vaccination. This will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day or 20 mg/day whichever is the maximum dose for paediatric subjects, or equivalent. Inhaled and topical steroids are allowed**.**
  - Administration of antineoplastic or immunomodulating agents or radiotherapy within 90 days prior to informed consent.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
- History of any reaction or hypersensitivity likely to be exacerbated by any medicinal products or medical equipment whose use is foreseen in this study.
- Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
- Known contact to an individual with any laboratory-confirmed *N. meningitidis* infection within 60 days, prior to enrolment.
- History of neuroinflammatory or autoimmune condition.
- Recurrent history or un-controlled neurological disorders or seizures.

6.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine(s) during the period starting 30 days before the informed consent or planned use during the study period.
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 180 days before the informed consent or planned administration during the study period.
- Previous vaccination with any group B meningococcal vaccine at any time prior to informed consent and assent as applicable (according to the subject's age).
- Previous vaccination with two doses of quadrivalent meningococcal conjugate vaccine (MenACWY*, Menveo, Menactra* or *MenQuadfi*).

6.2.3. Prior/Concurrent clinical study experience

- Subject concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device), will not be enrolled.

6.2.4. Other exclusions

- Child in care

  Please refer to section 12.1.2 for the definition of child in care.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- Any study personnel or immediate dependants, family, or household member.

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

6.3. Criteria for temporary delay for vaccination

Vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as body temperature ≥ 38.0°C (100.4°F). The preferred location for measuring temperature in this study will be the oral cavity.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.
- Use of antipyretics and/or analgesic medications within 6 hours prior to vaccination.
- Significant acute illness within the previous 7 days.
- Administration of any other vaccine 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to and after each vaccination*.

  *In case emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is organised by public health authorities outside the routine immunisation programme, the time period described above can be reduced if, necessary for that vaccine, provided it is licensed and used according to its Product Information.
- A positive test for active COVID-19 within the previous 14 days. The testing should be done using a molecular assay (polymerase chain reaction [PCR]) or antigen test approved by the country regulatory authorities.

- Subjects with known COVID-19 positive contacts in the past 14 days.

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

6.4. Screen and baseline failures

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

7. TREATMENTS

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

7.1. Treatments administered

The candidate vaccine to be used has been developed and manufactured by GSK.

The study vaccines specific to this study are described below.

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

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

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

Commercial vaccines are assumed to comply with the specifications given in the manufacturer’s currently approved dossier.

Table 9 Treatments administered

Study Treatment Name:	***Bexsero***	***Menveo****		**Placebo**
Vaccine(s)/Product(s) name	rMenB+OMV NZ	MenA lyo	MenCWY liquid	Placebo (NaCl)
Presentation	Suspension for injection_Suspension for suspension for injection in a syringe	Powder for solution for injection in a vial	Solution for solution for injection in a vial	Solution for injection in a syringe
Vaccines formulation	CCI [redacted]	[redacted]	[redacted]	Sodium chloride (NaCl) (0.9%); Water for injections
Product Category	Combination Product	Biological Product		Combination Product
Route of Administration	Intramuscular use	Intramuscular use		Intramuscular use
Administration site:				
Location	Deltoid	Deltoid		Deltoid
Laterality*	Left/Right****			
Number of doses to be administered:	2	1		1
Volume to be administered**	0.5 mL	0.5 mL		0.65 mL*****
Packaging and Labelling **Do not include a sample of the label text or details of pack design in the protocol. It will be specified in the SPM**	Refer to SPM for more details	Refer to SPM for more details		Refer to SPM for more details
Manufacturer	GSK	GSK		GSK

* The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

** Refer to the SPM for the volume after reconstitution, if applicable.

*** CCI [redacted]

**** Laterality information per visit/ group/treatment is provided in Table 10.

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

Table 10 Administration and Laterality

Type of contact and timepoint	Study group	Treatment name	Laterality*
Visit 1 (Day 1)	MenB+MenACWY	rMenB+OMV NZ	Left
		MenACWY	Right
	MenB	rMenB+OMV NZ	Left
		Placebo	Right
	MenACWY	MenACWY	Left
		Placebo	Right
Visit 3 (Day 61)	MenB+MenACWY	rMenB+OMV NZ	Left
	MenB	rMenB+OMV NZ	Left
	MenACWY	rMenB+OMV NZ	Left
Visit 4 (Day 91)	MenB+MenACWY	Placebo	Left
	MenB	MenACWY	Left
	MenACWY	rMenB+OMV NZ	Left

*Laterality is defined due to multiple vaccinations at different visits; non-dominant arm is the preferred arm for injection, when applicable. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

- Study vaccination will be performed on Day 1 (Visit 1), Day 61 (Visit 3) and Day 91 (Visit 4).
- All subjects will undergo a physical exam and safety related assessments at each Visit (5 clinic visits on study days 1, 31, 61, 91 and 121, respectively).
- After completing all prerequisite procedures prior to vaccination, vaccines should be administered by unblinded study personnel as a deep intramuscular (IM) injection, preferably into the deltoid area of the arm. To be able to efficiently distinguish local AEs after the concomitant vaccination at study Day 1 (Visit 1), the 2 injections will be separately administered into both arms. The second and third study vaccination occurring at study Day 61 (Visit 3) and study Day 91 (Visit 4) will be preferably administered into the deltoid area of the non-dominant arm. The exact anatomic location of each injection must be carefully recorded in the Medical Chart and in the eCRF (refer to Section 7.1 for detailed description of the vaccines administration procedure).

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccines administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 4).

The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis and syncope.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine and report the issue to the manufacturer. For rMenB+OMV NZ and MenACWY vaccines the issue should be reported as a Pharmaceutical Technical Complaint. The vaccine should not be discarded until authorized by GSK. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Detailed vaccine preparation and administration instructions will be provided to investigators in the Clinical Trials Supply Manual prior to study start.

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

An overdose would also occur if 2 doses of the study vaccine are administered within half the time of the recommended interval between doses, as defined in the protocol.

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

7.2. Method of treatment assignment

7.2.1. Subject identification

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

7.2.2. Randomization of treatment

7.2.2.1. Randomization of supplies

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

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

7.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by component.

7.2.2.2.1. Study group and treatment number allocation

The target will be to enroll approximately 945 eligible subjects who will be randomly assigned to 3 study groups in a 1: 1: 1 ratio (approximately 315 subjects in each group).

Subjects will be randomized in the source data base for internet randomization system (SBIR) system to one of the 3 parallel treatment arms in a 1:1:1 ratio to receive:

- Group MenB+MenACWY: rMenB+OMV NZ given concomitantly with MenACWY at study Day 1; rMenB+OMV NZ at study Day 61; Placebo at study Day 91.
- Group MenB: rMenB+OMV NZ given concomitantly with Placebo at study Day 1; rMenB+OMV NZ at study Day 61; MenACWY at study Day 91.
- Group MenACWY: MenACWY given concomitantly with Placebo at study Day 1; rMenB+OMV NZ at study Day 61 and at study Day 91.

The Subject ID will be the subject's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study.

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a minimization procedure accounting for center.

After obtaining the signed/witnessed/thumb printed and dated ICF/IAF from the subject/ subject's parent/ LAR and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for each component.

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

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

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure and the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrolment Log and in the source document as specified in the Source Documentation Agreement Form (SDA). The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 6.4.

If for any reason, after randomization the subject fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures.

Note: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the SBIR system will use the forced randomization procedure in order to continue to enroll and vaccinate subjects. The system moves seamlessly to the next treatment in the minimization algorithm arm for which the vaccine supplies are available. The site will not be aware of the forced randomization event.

7.2.2.2.2. Treatment number allocation for subsequent doses

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

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

7.3. Blinding and unblinding

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccines recipient and those responsible for the evaluation of any study endpoint (e.g. safety and reactogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by qualified healthcare professional who will not participate in any of the study clinical evaluations.

The laboratory in charge of the laboratory testing will be blinded to the treatment as well as to the subject number. In addition, a different subject code will be used for each timepoint tested. This subject coding will prevent the laboratory from linking the consecutive visits to a specific subject.

The serological data, which would lead to the unblinding of the study groups, will not be available during the course of the study to any investigator or any person involved in the clinical conduct of the study (including data cleaning).

7.3.1. Emergency unblinding

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

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

As back up process, the investigator has the option of contacting a GSK Helpdesk (refer to Table 11) if he/she needs support to perform the unblinding (i.e., he/she cannot access the automated Internet-based system).

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

Table 11 Contact information for emergency unblinding

GSK Helpdesk 24/24 hour and 7/7 day availability
The Helpdesk is available by phone, fax and email Phone: +32.2.656.68.04 For US only Toll Free: + 1 844 446 3133 Italy Toll Free: 800 879 197 For Canada, US and Puerto Rico Alternate Toll-free number: 877.870.0019 Fax: +32.2.401.25.75 email: rix.ugrdehelpdesk@gsk.com

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

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

7.4.1. Storage and handling of study vaccines

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

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

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

Study vaccines that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g., Site Monitor).

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

The Sponsor will ensure the following:

- Supply the study vaccines.
- Appropriate labelling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
- Appropriate use of the study vaccines, including:
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.

- Appropriate documentation of administration of vaccines to study subjects including:

  Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.

  Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.

- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Copy of destruction Certificate

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.4.2. Replacement of unusable vaccine doses

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

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

7.5.1. Recording of concomitant medications/products and concomitant vaccinations *(Amended 11 October 2022)*

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

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

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period of 30 days post-vaccination.
- Relevant medications/products administered during the period (Day 1 to Day 451) ***or (Day 1 to Day 271) for subjects who have not reached Day 271 at the time this amendment takes effect.***
- Any concomitant vaccination administered in the period starting 14 days before the first dose of study vaccines and ending at the last study contact (Day -14 to Day 451) ***or (Day 1 to Day 271) for subjects who have not reached Day 271 at the time this amendment takes effect.***
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement]. The preferred location for measuring temperature in this study will be the oral cavity.
- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the subject from the study. Please refer to the section 7.5.2 for further details.
- Any concomitant medications/products/vaccines relevant to an SAE/Adverse Event of Special interest (AESI) to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/AESI. In addition, concomitant medications relevant to SAEs and AESI's need to be recorded on the expedited Adverse Event report.
- The use of antipyretic and/or other medications to prevent (prophylactic use) and/or treat fever during the first 7 days after vaccination to be recorded in the eCRF as well.
- The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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

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

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period.
- Immunosuppressants or other immune-modifying drugs defined as follows:
  - Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed. This will mean prednisone ≥20 mg/day (for adult subjects) or ≥0.5 mg/kg/day or 20 mg/day whichever is the maximum dose for paediatric subjects, or equivalent. Inhaled and topical steroids are allowed**.**
  - Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Immunoglobulins and/or any blood products administered during the study period.
- Investigational or non-registered medicinal products within 30 days prior to informed consent/assent.
- Drug and/or alcohol abuse.

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

At each study visit subsequent to the first vaccination/the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition that may lead to elimination from per protocol analysis. If it is the case, the condition(s) must be recorded in the eCRF.

7.7. Contraindications to subsequent vaccine(s) administration

Prior to receipt of additional study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects meet any of the original exclusion criteria or the criteria listed below, they should not receive additional vaccinations. However, these subjects should be encouraged to continue study participation.

- Anaphylaxis following the administration of vaccines
- Pregnancy (see Section 12.5.7.1)
- Any condition that in the judgment of the investigator would make IM injection unsafe.

- Any occurrence of an event listed in the exclusion criteria which must be always re-assessed by the investigator before administration of the second dose of study vaccine.
- Subjects who experience any serious adverse event (SAE) judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Occurrence of a new AESI or the exacerbation of an existing AESI. Refer to Section 12.5.5 for the definition of AESIs.

7.8. Warnings and precautions

Warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to the approved product label/package insert.

7.9. Treatment after completion of the study

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

Procedures conducted as part of the subject's routine clinical management (e.g. blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

8.1. General study aspects

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

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems in a uniform fashion and sites will be monitored to ensure consistency in study execution across all centers.

During special circumstances, exemplified by the COVID-19 pandemic, certain study procedures may be adapted to protect the subject and promote data integrity. Refer to Section 8.7 for further details.

8.2. Pre-vaccination procedures

8.2.1. Data Collected from Subjects

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

- Demographic Information.
- Medical history (any significant past diagnoses including allergies, hospitalizations, surgeries requiring in-patient hospitalization, any other medical conditions which may impair the assessment of safety of the rMenB+OMV NZ and MenACWY vaccines).
- Vaccination history as confirmed by vaccination records, if accessible.
- Pre-vaccination body temperature.
- Post-vaccination immediate reactions observed for at least 30 minutes after injection: signs or symptoms of anaphylaxis, allergic phenomena (such as rashes, itching, or other allergic manifestations). Local and systemic solicited data (including e.g., use of medication to treat or prevent fever, and/or pain).
- Post-vaccination solicited local and systemic AEs collected at home by subject and/or subject's parent(s)/LAR(s) and recorded on Subject Diary (eDiary) for 7 days following each vaccination visit.
- Adverse Events.
  - Unsolicited AEs occurring within 30 days after each vaccination will be collected for all subjects by interviewing the subject and/or subject's parent(s)/LAR(s) (as applicable) during the site visits or Safety Follow-up Calls and by reviewing of available medical records.
  - SAEs occurring during the entire study period

  - Medically attended AEs occurring during the entire study period
  - AEs leading to premature withdrawal from the vaccination/study occurring during the entire study period
  - AESI occurring during the entire study period (for subjects who received rMenB+OMV NZ)
- Prior and concomitant medication as defined in Section 7.5.

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

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

8.2.2. Collection of demographic data

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

8.2.3. Medical history

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

Medical history will be collected at Visit 1, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications (refer to Section 7.5.2), 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.

Review of systems is a structured interview that queries the subject/subjects' parent(s)/LAR(s) as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide physical examination.

8.2.4. Physical examination

Physical examination is to be performed by a qualified health care professional. "Qualified health care professional" refers to a licensed or certified health care professional with documented training and experience, as determined by the Principal Investigator (PI), and who is permitted by institutional policy to perform protocol required procedures, and who is identified on the Study Staff Signature Log.

The physical examination of the subject will include assessment of body temperature (preferably oral) and resting vital signs: systolic/diastolic blood pressure and heart rate after at least 10 minutes of rest.

Medical history-directed physical examination to assess eligibility will be performed during Visit 1.

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

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

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

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

8.2.5. Pregnancy test

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

Urine will be collected for pregnancy testing in females of child-bearing potential, before vaccination at Visits 1, 3, and 4, and the results recorded in the source document and the eCRF.

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

8.2.6. Pre-vaccination body temperature

The body temperature (preferably oral) of each subject needs to be measured prior to any study vaccines administration. If the subject has fever [fever is defined as 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 (see Table 4 and Section 6.3).

8.3. Efficacy assessments

Please refer to the SPM and central laboratory manual for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that further findings may make it desirable to use the samples acquired in this study for further research, not described in this protocol. Therefore, all subjects/subjects parent (s)/LAR(s) will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for further research. Further research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

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

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

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

If additional testing is performed, the marker priority ranking given in Section 8.3.4 may be changed.

CCI [redacted]

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

8.3.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the

exclusion of the subject from the per-protocol analysis (See Section 10.2 for the definition of populations for analyses). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM or the central laboratory manual**.**

The above applies to any external partners designated by GSK as well.

8.3.2. Biological samples

Blood samples will be collected from all subjects for serology evaluation. Refer to the Module on Biospecimen Management in the SPM or central laboratory manual for detailed instructions for the collection, handling and processing of the samples.

8.3.2.1. Blood sampling for immunogenicity response assessments

Blood samples will be taken during certain study visits as specified in Section 2.

- Before vaccination a blood sample will be obtained at Visit 1 and Visit 4 for serologic evaluation.
- A volume of approximately 20 mL of whole blood should be drawn from all subjects before first vaccination (Visit 1, study Day 1), 1 month after the first vaccination (Visit 2, study Day 31) and 1 month after the second vaccination and before the third vaccination (Visit 4, study Day 91) for immunogenicity evaluation. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM and the central laboratory manual for more details on sample management and storage conditions.
- The total amount of blood collected over the study period per subject will be approximately 60 mL.

A topical anesthetic (e.g. EMLA adhesives or cream) may be used at the site of blood sample draw, according to local practice in order to minimize pain.

The blood will be processed, identified and stored according to the Central Laboratory manual.

In clinic visits where a blood draw and a vaccination are planned, ensure that all samples collected for immunogenicity assessments are taken prior to any vaccination. The following are clinical circumstances that warrant delay of blood samples collection for immunogenicity assessments in this study:

- Receipt of systemic antibiotics within the previous 3 days (72 hours) before blood sample collection at Visit 1, Visit 2 and Visit 4.

In the event that a subject meets the criterion for delay of blood samples collection, blood samples collection may proceed once the appropriate window for delay has passed and

vaccination may be delayed as appropriate to ensure sample collection prior to vaccination.

Table 12 Biological samples

Sample type	Quantity	Unit	Timepoint	Subject/Group	Day
Blood	Approximately 20	mL	Visit 1 (Pre-Vacc I)	All	1
			Visit 2 (Post Vacc1)		31
			Visit 4 (Post Vacc2)		91

8.3.2.2. Other biological samples

Urine sampling: Urine test is the preferable method to test pregnancy. Urine will be collected for pregnancy testing in females of child-bearing potential, before each vaccination at Visits 1, 3, and 4, and the results recorded in the source document and eCRF.

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

8.3.3. Laboratory assays

The measures of immunogenicity used in this study are standard, i.e., widely accepted and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The immunogenicity of the rMenB+OMV NZ and of MenACWY vaccines will be assessed in this study by measuring the serum bactericidal activity which is a functional measure of the ability of antibodies, in conjunction with human complement, to kill meningococci, and is widely accepted and generally recognized as the serological surrogate of protection.

The induction of antibodies directed against serogroup A, C, W, and Y meningococci following MenACWY vaccination will also be measured by Enzyme-Linked Immunosorbant Assay (ELISA). The ELISA procedure is used to detect the amount of sera immunoglobulin G (IgG) antibody in response to *N. meningitidis* polysaccharide antigens.

Please refer to Appendix 2 for a detailed description of the assays performed in the study.

Please refer to Appendix 3 for the address of the clinical laboratories used for sample analysis.

Serological testing for immunogenicity to rMenB+OMV NZ and to MenACWY vaccines will be performed at GSK Biologicals' laboratories or in a laboratory designated by GSK Biologicals using standardized and validated procedures (refer to Table 13).

Table 13 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/Manufacturer	Unit*	LOD*	LLOQ*	Laboratory**
SER	Neisseria meningitidis B M14459 (fHbp) Ab	hSBA	In house	1/DIL	3	5	GSK*** or laboratory designated by GSK Biologicals
	Neisseria meningitidis B 96217 (NadA) Ab				6	15	
	Neisseria meningitidis B NZ98/254 (PorA) Ab				4	6	
	Neisseria meningitidis B M07-0241084+ (NHBA) Ab				4	4	
SER	Neisseria meningitidis Serogroup A 3125 Ab	hSBA	In house	1/DIL	4	5	
	Neisseria meningitidis Serogroup C C11 Ab				4	6	
	Neisseria meningitidis Serogroup W 240070 Ab				4	7	
	Neisseria meningitidis Serogroup Y 860800 Ab				4	6	
SER	N men Serogroup A Ab.IgG	ELISA∞	TBD	µg/mL	TBD	TBD	
	N men Serogroup C Ab.IgG				TBD	TBD	
	N men Serogroup W Ab.IgG				TBD	TBD	
	N men Serogroup Y Ab.IgG				TBD	TBD	

Ab: Antibody; IgG: Immunoglobin G; µg: Microgram, ml: Milliliter, DIL: Dilution, SER: Serum, 1/dilution: reciprocal of the dilution; LOD: Limit of detection; LLOQ: Lower limit of quantitation, ELISA: enzyme-linked immunosorbent assay; TBD = to be determined.

*Strain, assay cut-off(s) and unit(s) might be subject to change during the course of 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.

**Refer to Appendix 3 to for the laboratory addresses.

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

+ The NHBA indicator strain, M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

∞For each of the MenACWY serogroups, ELISA assay cut-offs will be determined following validation of the assay. This will be documented in the clinical report.

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

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

8.3.4. Biological samples evaluation

8.3.4.1. Immunological read-outs

Table 14 Immunological read-outs *(Amended 11 October 2022)*

Blood sampling timepoint		Subset/Sub-cohort Name	No. of subjects	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Vacc	***Group MenB+MenACWY***	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084**** ***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY***
		Group MenB	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****
		Group MenACWY	***315***	***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY***
Visit 2 (Day 31)	Post Vacc1	***Group MenB+MenACWY***	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084**** ***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY*** ***ELISA IgG anti meningococcal A, C, W, Y***
		Group MenB	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****
		Group MenACWY	***315***	***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY*** ***ELISA IgG anti meningococcal A, C, W, Y***
Visit 4 (Day 91)	Post Vacc2	***Group MenB+MenACWY***	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****
		Group MenB	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****

*The NHBA indicator strain M07-0241084 may be subject to change during the study before clinical testing starts. In this case, this change will be documented in the clinical report.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 14.

8.3.5. Immunological correlates of protection

For the *N. meningitidis* serogroup C antigen in the MenACWY vaccine**,** an immunological Correlate of Protection (CoP) has been established as ≥ 1:4 hSBA.

No generally accepted immunological CoP has been demonstrated so far for the other antigen(s) used in the candidate vaccine(s).

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

Refer to the section 7.9 for details regarding treatment for non-responders.

8.4. Safety Assessments

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

The measures of safety used in this study are routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic AEs routinely monitored in vaccine clinical studies as indicators of reactogenicity.

8.4.1. Safety definitions

Please refer to Section 12.5 for safety definitions.

8.4.2. Follow-up Clinic Visit

Follow-up clinic visits will be performed on study Days 31 (Visit 2), 91 (Visit 4) and 121 (Visit 5).

During the follow-up clinic visit on study Days 31 (Visit 2), 91 (Visit 4) and 121 (Visit 5), the eDiary will be reviewed by the staff. Study-specific requirements are described in the SPM. At last Follow-Up clinic visit (Day 121), the eDiary should be returned to the study site and collected. For details on the eDiary see Section 12.5.8.

The subject and/or parent(s)/LAR(s) will be interviewed to determine if any unsolicited AEs occurred and if any concomitant medications associated with those events or vaccines were taken/received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present. AEs reported by the subject and/or parent(s)/LAR(s) at this follow-up clinic visit must be

recorded in the subject's source document and on an Adverse Events eCRF, as specified in Section 8.4.

Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, concomitant medication use. This assessment may include measurement of vital signs, body temperature (preferably oral) and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy (see glossary of terms for definition of a qualified healthcare provider). Any relevant clinical finding (when deemed abnormal) resulting from the symptom-directed physical examination should be documented in the subject's source document and eCRF(s).

Approximately 20 mL of blood will be drawn from all subjects for immunological evaluation at Visit 1 (Day 1), Visits 2 (Day 31) and Visit 4 (Day 91). Refer to Section 8.3.2.

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

8.4.3. Safety Follow-up calls *(Amended 11 October 2022)*

A total of seven safety follow-up calls will be performed. Safety follow-up calls will be performed on Day 15, Day 75, Day 105, Day 181, Day 271, Day 361 and Day 451 (study termination). ***For subjects who have not reached Day 271 at the time this amendment takes effect, a total of five safety follow-up calls will be performed. Safety follow-up calls will be performed on Day 15, Day 75, Day 105, Day 181, and Day 271 (study termination).***

Safety follow-up calls are calls made to the subject by a qualified healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject/subject's parent(s)/LAR(s) will be interviewed according to the script, and information relating to unsolicited adverse events [including SAEs, adverse events of special interest (AESIs), medically attended adverse events, and/or AEs leading to withdrawal] and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

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

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

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

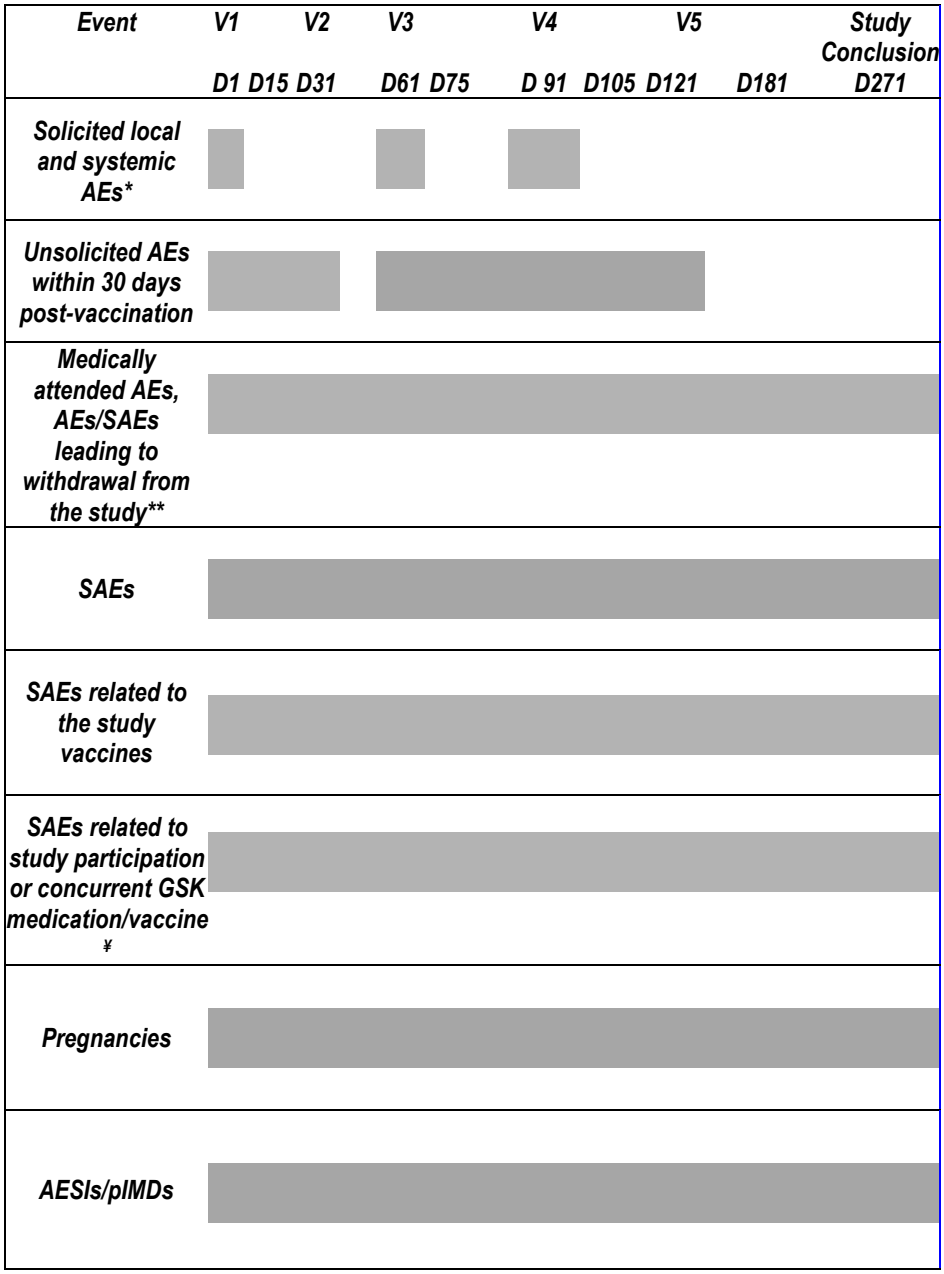
An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in is given in Table 15. Refer to the Section 12.5.8.2 for details on the time period for recording safety information.

Table 15 Reporting periods for collecting safety information *in subjects who have crossed D271 (Amended 11 October 2022)*

Event	V1		V2	V3		V4		V5				Study Conclusion
	D1	D15	D31	D61	D75	D 91	D105	D121	D181	D271	D361	D451
Solicited local and systemic AEs*												
Unsolicited AEs within 30 days post-vaccination												
Medically attended AEs, AEs/SAEs leading to withdrawal from the study**												
SAEs												
SAEs related to the study vaccines												
SAEs related to study participation or concurrent GSK medication/vaccine¥												
Pregnancies												
AESIs/pIMDs												

AE: Adverse event, AESI: adverse event of special interest, D: Day, SAE: Serious adverse event, V: Visit.
*Solicited AEs to be collected for 7 days following each vaccination, with ongoing solicited AEs collected until resolution or day 30, whichever occurs first.
** Including COVID-19 infection related AEs.
¥Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a parent(s)/LAR(s) or participant signs the consent form to the end of the study

Table 16 Reporting periods for collecting safety information in subjects who have not reached D271 (*Amended 11 October 2022*)



AE: Adverse event, AESI: adverse event of special interest, D: Day, SAE: Serious adverse event, V: Visit.
**Solicited AEs to be collected for 7 days following each vaccination, with ongoing solicited AEs collected until resolution or day 30, whichever occurs first.*
*** Including COVID-19 infection related AEs.*
¥Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a parent(s)/LAR(s) or participant signs the consent form to the end of the study

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Appendix 5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 15. Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccines, the investigator will promptly notify the Study Contact for Reporting SAEs.

For further details, please see Section 12.5.11.1.2.

8.4.5. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5.8.

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

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

Table 17 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

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

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

8.4.6.1. Contact information for reporting of serious adverse events (SAEs), AESIs, pregnancies and study holding rules

Table 18 Contact information for reporting of serious adverse events (SAEs), AESIs, and pregnancies

Study contact for questions regarding SAEs, AESIs, and pregnancies
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, AESIs, and pregnancies
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com US sites Fax: 1-610-787-7053 Canadian sites only Fax: 1-866-903-4718

8.4.6.2. Regulatory reporting requirements for SAEs

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

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

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

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

All SAEs must be reported by the investigator to his/her corresponding EC/ IRB or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

8.4.7. Medical device deficiencies

Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is:
An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

The study intervention is a combination product constituted of a device and biologic product (e.g. pre-filled syringes). Refer to the Glossary of terms for the definition of combination product and medical device deficiency.

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

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

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 12.7 for definitions and details on recording and reporting of these events.

The sponsor will be the contact for the receipt of device deficiency reports.

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 GSK within 24 hours.

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 fulfil 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 Section 12.7.3 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.

8.4.8. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 12.5.5), will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.5.11**.**

8.4.9. Treatment of adverse events

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

8.4.10. Subject card

Study subjects/subjects' parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

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

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

8.5. Genetic Research (Pharmacogenetics)

Genetics are not evaluated in this study.

8.6. Study conclusion

- The study termination call will occur on study Day 451 (after safety follow up call 7) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 [Month 9] at the time this amendment takes effect.*** The termination visit will be a phone call (***Amended 11 October 2022***).

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

- At the Termination visit, the following procedures will be performed: interview of subject and/or parent(s)/LAR(s) to collect any medically attended AEs, AEs leading to withdrawal, AESI, SAEs, and/or concomitant medications/vaccinations. Any concomitant medications associated with those events will also be collected and recorded in the subject's records and on the eCRF.
- The site will review with the subject and/or parent(s)/LAR(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider if the subject and/or parent(s)/LAR(s) chooses to share this information or if it is required by local regulations.
- The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

8.6.1. Early Termination

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation.

During the telephone call, the following procedures will be performed:

- review of Subject eDiary (if applicable).
- interview of subject and/or parent(s)/LAR(s) to collect unsolicited AEs, medically attended AEs, AEs leading to withdrawal, SAEs, AESI.
- interview of subject and/or parent(s)/LAR(s) to collect concomitant medications/vaccinations administered to treat AEs collected in the study.

Additionally, the following 2 procedures will be performed at the clinic visit:

- perform a symptom-directed physical assessment (including e.g., measurement of vital signs, body temperature [preferably oral] and a check of general appearance).
- blood sampling to test immunogenicity (if withdrawal occur at or prior to Visit 4 [study Day 91]).

If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

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

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

8.7. Study procedures during special circumstances

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

- If the eDiary device was provided to the subject, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 5).
- Biological samples may be collected at a different location* other than the study site or at subject's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

*It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on subjects by investigator and staff at a site other than the designated study site. Refer to local regulatory guidance on conduct of clinical trials during COVID-19.

Impact on the Per Protocol Set (PPS) for immunogenicity will be determined on a case by case basis.

9. DISCONTINUATION CRITERIA

9.1. Discontinuation from the study

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

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

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

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Primary reason for study withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by

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

- SAEs requiring expedited reporting (please refer to section 12.5.9.2 for the details)
- Unsolicited non-serious AE
- Solicited adverse event
- Protocol deviation
- Withdrawal by subject, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 12.5.11).

The reasons for premature withdrawal from the study include adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event:

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

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

Death:

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

Withdrawal of consent:

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

If a subject and/or parent(s)/LAR(s) withdraw(s) consent but does not revoke the HIPAA (The Health Insurance Portability and Accountability Act) authorization, the Sponsor will have full access to the subject's medical records, including termination visit information. If a subject and/or parent(s)/LAR(s) revokes only the HIPAA authorization, the Sponsor will have full access to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up:

For subjects who are not accessible through call for final visit (study Day 451), or for 2 consecutive visits, study staff are encouraged to make at least 3 documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject and/or parent(s)/LAR(s) to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject. Please refer to Section 9.3 for further details.

Administrative Reason:

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

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

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

Protocol Deviation:

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

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

Any subject who becomes pregnant during the study, despite the protocol requirement for highly effective method of contraception, will not receive further vaccinations but should be encouraged to continue participating in the study for safety follow-up. The site must complete a Pregnancy Report eCRF (initial report) as soon as possible after learning of pregnancy occurrence (see Section 12.5.8 for further details). If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of follow-up period.

9.2. Discontinuation of study vaccine(s)

A 'withdrawal' from the study vaccine(s) refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine(s) may continue further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

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

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

9.3. Lost to follow-up

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

The target sample size is 750 subjects evaluable for immunogenicity (250 subjects per study group). Evaluable subjects mean all subjects included in the set for the primary statistical analysis defined in Section 10.2) Considering that approximately 20% of the enrolled subjects might withdraw or not be evaluable for immunogenicity, the target sample size to be enrolled is 945 subjects (315 subjects per study group). These sample sizes were calculated based on the standard deviations from corresponding treatments in the mentioned studies, the non-inferiority margin of 0.5 and the expected ratio GMR of the GMTs (or GMCs) of 0.9.

10.1.1. Hypotheses related to primary and secondary objectives

10.1.1.1. Primary Immunogenicity Objectives

The statistical hypotheses and analyses are based on the common assumption that the logarithmically (base of 10) transformed hSBA titers are normally distributed.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY to rMenB+OMV NZ

The null (not non-inferiority) and the alternative (non-inferiority) hypotheses are:

$$H_{0,i}^{MenB}: \mu_{A,MenB,i} - \mu_{B,MenB,i} \leq \log_{10}(0.5)$$ versus
$$H_{1,i}^{MenB}: \mu_{A,MenB,i} - \mu_{B,MenB,i} > \log_{10}(0.5)$$,

where i=1,…,4 is an index over the four serogroup B strains M14459, 96217, NZ98/254 and M07-0241084, and $\mu_{A,MenB,i}$ and $\mu_{B,MenB,i}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the i[th] serogroup B strain at one month after the second vaccination in Groups MenB+MenACWY and MenB respectively.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY to MenACWY

The null (inferiority) and the alternative (non-inferiority) hypotheses are:

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} \leq \log_{10}(0.5)$$ versus

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} > \log_{10}(0.5)$$,

where j=1,…,4 is an index over the four serogroups A, C, W and Y, and $\mu_{A,MenACWY,j}$ and $\mu_{C,MenACWY,j}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the j[th] MenACWY serogroup at one month after the first vaccination in Groups MenB+MenACWY and MenACWY respectively.

The threshold of $\log_{10}(0.5) = -\log_{10} 2 \approx -0.3$ is the non-inferiority margin.

The choice of non-inferiority margin of 0.5 for the assessment of GMT ratios for the four serogroup B test strains is based on previous clinical study results (post-vaccination GMTs) showing that individual titers would, on average, remain protective for all 4 strains if individual titers were reduced to half (see section 10.1).

The non-inferiority margin of 0.5 for the assessment of GMT ratios for the MenACWY serogroups was found appropriate in view of the Center for Biologics Evaluation & Research (CBER) concurrence with the 2-fold equivalence margin (for a lot-to-lot consistency study) at the End-of-Phase II meeting in 2006.

The 8 hypotheses associated with the primary objective will be tested simultaneously, to control for the type I error rate. The testing of the hypotheses will be done simultaneously on all the strains and serogroups .

10.1.1.2. Secondary Immunogenicity Objectives

There is a non-inferiority test associated with the concomitant rMenB+OMV NZ with MenACWY to MenACWY using ELISA GMCs.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY to MenACWY

The null (inferiority) and the alternative (non-inferiority) hypotheses are:

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} \leq \log_{10}(0.5)$$ versus

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} > \log_{10}(0.5),$$

where j=1,…,4 is an index over the four serogroups A, C, W and Y, and $\mu_{A,MenACWY,j}$ and $\mu_{C,MenACWY,j}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the jth MenACWY serogroups at one month after the first vaccination in Groups MenB+MenACWY and MenACWY respectively.

Non-inferiority of concomitant rMenB+OMV NZ with MenACWY versus MenACWY alone will be claimed if the null hypotheses are rejected for all four serogroups A, C, W and Y, as measured by ELISA GMCs.

10.1.2. Sample size calculation

For the immune response to rMenB+OMV NZ, sample size calculations are based on hSBA titer data from the GSK V102_03 and V72_41 studies and for the immune response to MenACWY, data from GSK V59P13E1 study and V102_02 study (ELISA GMCs) is used.

Sample size/power calculations are based on specific fixed values for the

- non-inferiority margin,
- standard deviations of (the distributions of) the logarithmically transformed (base of 10) hSBA titers for the strains M14459, 96217, NZ98/254 and M07-0241084.
- standard deviations of (the distributions of) the logarithmically transformed (base of 10) hSBA titers for the serogroups A, C, W and Y,
- ratios of the GMTs medians of (the distribution of) the hSBA titers for strains M14459, 96217, NZ98/254 and M07-0241084 when rMenB+OMV NZ is administered with MenACWY versus when rMenB+OMV NZ is administered alone (one ratio per strain),
- ratios of the GMTs/GMCs of (the distribution of) the hSBA titers for the serogroups A, C, W and Y when MenACWY is administered with rMenB+OMV NZ vs when MenACWY is administered alone (one ratio per serogroup).

Standard Deviations for hSBA Titer:

In Table 19 the standard deviations are listed that were used in the power calculation, along with the 80% upper limit of the confidence interval (CI) for standard deviation.

For the primary objective 1, hypothesis 1, testing of rMenB+OMV NZ when given concomitantly with MenACWY to rMenB+OMV NZ given alone, test of treatment Group MenB+MenACWY versus treatment Group MenB, the standard deviations from studies V102_03 and V72_41 were used.

For the primary objective 2, hypothesis 2, testing of MenACWY when given concomitantly with rMenB+OMV NZ to MenACWY given alone, test of treatment Group MenB+MenACWY versus treatment Group MenACWY, the standard deviations from study V59P13E1 GrIV_V were used.

For the secondary objective, hypothesis 3, testing of MenACWY when given concomitantly with rMenB+OMV NZ to MenACWY given alone based on ELISA GMCs, test of treatment Group MenB+MenACWY versus treatment Group MenACWY, the standard deviations from study V102_02 were used.

Table 19 Observed SDs with the Upper Limits of the Two-Sided 80% CI for the Logarithmically (base of 10) Transformed hSBA Titers

Hypothesis	study	strain	sd	N	alpha	df	Est_sd
1	V102_03	M14459	0.65413	92	0.2	91	0.72443
1	V72_41	96217	0.25408	30	0.2	29	0.30774
1	V102_03	NZ98/254	0.56100	92	0.2	91	0.62129
1	V102_03	M07-0241084	0.55235	92	0.2	91	0.61171
2	V59P13E1GrIV_V	MenA	0.46542	119	0.2	118	0.50866
2	V59P13E1GrIV_V	MenC	0.54356	117	0.2	116	0.59455
2	V59P13E1GrIV_V	MenW	0.57507	118	0.2	117	0.62875
2	V59P13E1GrIV_V	MenY	0.59519	118	0.2	117	0.65075
3	V102_02	MenA	0.67891	59	0.2	58	0.77338
3	V102_02	MenC	0.56615	59	0.2	58	0.64493
3	V102_02	MenW	0.50023	57	0.2	56	0.57128
3	V102_02	MenY	0.53432	58	0.2	57	0.60943

The testing of the hypotheses will be done simultaneously on all the strains and serogroups.

Power Calculation and Sample Size Results of the Non-inferiority Testing of rMenB+OMV NZ, First Primary Objective, Referred to as Hypothesis 1

In Table 20 the results are presented of the power calculation (in %) with T1 MenB strains M14459, 96217, NZ98/254 and M07-0241084 with sample size raising from 200 to 300 per treatment group. The individual power calculations are presented along with the power for all serogroup B strains. The power for rMenB+OMV NZ is the multiplication of the power for all 4 individual strains. A non-inferiority margin of 0.5 and a GMT ratio between treatments of 0.9 was used.

Table 20 Power (in %) for the Individual and for the Overall MenB Strains

Hypothesis	N	Power M14459	Power 96217	Power NZ98_254	Power M07_0241084	Power MenB
1	200	94.01	100	98.38	98.62	91.21
1	210	94.98	100	98.75	98.95	92.80
1	220	95.80	100	99.04	99.20	94.11
1	230	96.49	100	99.26	99.39	95.19
1	240	97.08	100	99.43	99.54	96.08
1	250	97.57	100	99.57	99.65	96.81
1	260	97.98	100	99.67	99.74	97.40
1	270	98.33	100	99.75	99.80	97.89
1	280	98.62	100	99.81	99.85	98.28
1	290	98.86	100	99.86	99.89	98.60
1	300	99.06	100	99.89	99.92	98.87

Power Calculation and Sample Size Results of the Non-inferiority Testing of MenACWY, Second Primary Objective, Referred to as Hypothesis 2

In Table 21 the results are presented of the power calculation (in %) with MenACWY with sample size raising from 200 to 300 per treatment group. The individual power calculations are presented along with the power for all MenACWY serogroups combined. The power for MenACWY is the multiplication of the power of all 4 individual

serogroups. A non-inferiority margin of 0.5 and a GMT ratio between treatments of 0.9 was used.

Table 21 Power (in %) for the Individual Serogroups and for the Overall MenACWY Serogroups

Hypothesis	N	Power MenA	Power MenC	Power MenW	Power MenY	Power MenACWY
2	200	99.88	98.99	98.17	97.46	94.60
2	210	99.92	99.24	98.58	97.98	95.79
2	220	99.95	99.43	98.90	98.40	96.72
2	230	99.97	99.58	99.15	98.74	97.45
2	240	99.98	99.69	99.34	99.01	98.02
2	250	99.99	99.77	99.49	99.22	98.47
2	260	99.99	99.83	99.61	99.39	98.82
2	270	99.99	99.87	99.70	99.52	99.09
2	280	100.00	99.91	99.77	99.62	99.30
2	290	100.00	99.93	99.83	99.71	99.46
2	300	100.00	99.95	99.87	99.77	99.59

Power Calculation and Sample Size Results of the Non-inferiority Testing of MenACWY, Secondary Objective, Referred to as Hypothesis 3

In Table 22 the results are presented of the power calculation (in %) with MenACWY using ELISA GMCs with sample size raising from 200 to 300 per treatment group. The individual power calculations are presented along with the power for all MenACWY serogroups combined. The power for MenACWY is the multiplication of the power of all 4 individual serogroups. A non-inferiority margin of 0.5 and a GMT ratio between treatments of 0.9 was used.

Table 22 Power (in %) for the Individual and for the Overall MenACWY Serogroups Using ELISA GMCs

Hypothesis	N	Power MenA	Power MenC	Power MenW	Power MenY	Power MenACWY
3	200	90.87	97.66	99.37	98.67	87.02
3	210	92.14	98.15	99.55	98.99	89.12
3	220	93.24	98.55	99.67	99.23	90.88
3	230	94.21	98.86	99.76	99.42	92.37
3	240	95.04	99.10	99.83	99.56	93.61
3	250	95.76	99.30	99.88	99.67	94.65
3	260	96.38	99.45	99.91	99.75	95.53
3	270	96.91	99.57	99.94	99.81	96.26
3	280	97.37	99.67	99.95	99.86	96.87
3	290	97.77	99.74	99.97	99.89	97.38
3	300	98.11	99.80	99.98	99.92	97.81

Power Calculation and Sample Size Results for all 3 Hypotheses Combined

In Table 23 the results are presented of the overall power (in %) when combining all, 3 hypotheses, consisting of 4 tests each. The overall power is the multiplication of the power of all 3 hypotheses as presented in Table 20, Table 21 and Table 22.

Table 23 Overall Power (in %) for the 3 Hypothesis Combined

N	Power Hypothesis 1	Power Hypothesis 2	Power Hypothesis 3	Power Overall
200	91.21	94.60	87.02	75.08
210	92.80	95.79	89.12	79.22
220	94.11	96.72	90.88	82.72
230	95.19	97.45	92.37	85.68
240	96.08	98.02	93.61	88.16
250	96.81	98.47	94.65	90.23
260	97.40	98.82	95.53	91.95
270	97.89	99.09	96.26	93.37
280	98.28	99.30	96.87	94.54
290	98.60	99.46	97.38	95.50
300	98.87	99.59	97.81	96.31

In summary to have an overall power of 90% or more, the minimum sample size need to be N=250 subjects per group. To account for a 20% drop out rate, N=315 subjects per group need to be enrolled. For the study, with 3 treatment groups, N=945 subjects need to be enrolled to have 750 eligible subjects.

10.2. Populations for analyses

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

Analysis Set	Description
Enrolled	All subjects who sign informed consent
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Full Analysis	All subjects who received at least 1 dose of the study treatment and have post-vaccination immunogenicity data
Per Protocol	All subjects who received at least 1 dose of the study treatment to which they are randomized and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion

10.3. Statistical analyses

10.3.1. Subjects disposition

Number of subjects enrolled, vaccinated subjects and completed will be described by group. Reason for early withdraw will be described by group. Full analysis and per-protocol analysis population set will be described by group.

10.3.2. Demography and baseline characteristics analyses

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

Distributions of subjects by sex, race, ethnic origin, geographical locations (US sites, non-US sites, if applicable) and according to the pre-vaccination hSBA titer (per strain, <LLOQ or ≥LLOQ) will be summarized overall and by Group.

10.3.3. Immunogenicity analyses

The primary analysis will be based on the Per Protocol Set of immunogenicity for the primary and secondary (non-inferiority) immunogenicity objective. If, in any study group, the percentage of enrolled or vaccinated subjects with serological results excluded from the per-protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set (FAS) will be performed to complement the per-protocol analysis. Supportive analyses using the FAS will also be performed for the primary immunogenicity endpoints.

Endpoint	Statistical Analysis Methods
Primary	**Within group assessment** • For Group MenB+MenACWY and Group MenB: hSBA GMTs for rMenB+OMV NZ against each of the four serogroup B test strains (M14459, 96217, NZ98/254 and M07-0241084*) at one month after the second vaccination for rMenB+OMV NZ (Visit 4) will be calculated. • For Group MenB+MenACWY and Group MenACWY: hSBA GMTs against each of the four serogroups A, C, W and Y for MenACWY at one month after the study vaccination of MenACWY (Visit 2) will be calculated. **Between group assessment** • The ratio of hSBA GMTs between Group MenB+MenACWY versus Group MenB when administered alone [Group MenB], at one month after the second vaccination of MenB will be calculated. • The ratio of hSBA GMTs between Group MenB+MenACWY versus Group MenACWY when administered alone [Group MenACWY], at one month after the (study) vaccination of MenACWY will be calculated.
Secondary	**Within groups assessment** • ELISA GMCs against each of the four serogroups A, C, W and Y at one month after the (study) vaccination of MenACWY for Groups MenB+MenACWY and MenACWY. The percentage of subjects (and 2-sided 95% Clopper-Pearson CIs) with hSBA titers ≥LLOQ for each and all serogroup B test strains at one month after the first and second vaccination for Groups MenB+MenACWY and MenB; and for serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY. • hSBA GMTs against each of the four serogroup B test strains at baseline and one month after first vaccination with rMenB+OMV NZ for Groups MenB+MenACWY and MenB. • hSBA GMRs (compared to baseline) against each serogroup B test strains at one month after the first and second vaccination for Groups MenB+MenACWY and MenB; and against serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY. • The percentage of subjects (and 2-sided 95% Clopper-Pearson CIs) with fourfold increase in hSBA titers relative to baseline for each serogroup B test strains at one month after the first and second vaccination for Groups MenB+MenACWY and MenB; and for serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY. **Between group assessment** • For all four serogroups A, C, W and Y, non-inferiority of the responses to MenACWY when given with rMenB+OMV NZ compared to MenACWY administered alone will be assessed in terms of ELISA GMCs. • The ratio of hSBA GMTs between Group MenB+MenACWY versus Group MenB when administered alone at one month after the first vaccination, will be calculated. • Between group differences (Group MenB+MenACWY vs Group MenB; and Group MenB+MenACWY vs Group MenACWY), at one month after the first and the second vaccination (as applicable) will be calculated, as well as their associated 95% CIs.
CCI [redacted]	

*The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

10.3.4. Safety analyses

All safety analyses will be performed on the exposed set.

Endpoint	Statistical Analysis Methods
Primary	**Analysis of Solicited Adverse events** • Frequencies and percentages of subjects experiencing each AE will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic AE overall and at each time point will also be presented. • Post-vaccination solicited AEs reported from Day 1 (of vaccination) to Day 7 will be summarized for the intervals Day 1-3, Day 4-7, Day 1-7 by maximal severity and by group, excluding the 30-minute measurement, which will be summarized separately. The severity of solicited local AEs, including injection-site erythema, induration, and swelling will be summarized according to categories based on linear measurements as presented in Table 29. • Injection site pain and systemic AEs (including fever) occurring up to 7 days after each vaccination will be summarized according to "mild", "moderate" or "severe". • Each solicited local and systemic AE will also be further summarized as "none" versus "any". Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. • Body temperature will be summarized by 0.5 °C increments from 38.0 °C/100.4°F up to ≥40 °C/104.0°F and will be broken down accordingly by route of measurement. **Analysis of Unsolicited Adverse Events** This analysis applies to all AEs occurring during the study, judged either as 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. All AEs 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 using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported AEs, as well as AEs judged by the investigator as possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and by interval of study observation. When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the group will be counted. Separate summaries will be produced for the following categories: • Serious adverse events (SAEs) • Adverse Events of Special Interest (AESIs) for subjects who received rMenB+OMV NZ • Adverse events that are possibly related to vaccine. • Adverse event leading to withdrawal. • Adverse events leading to a medically attended visit. • Data listings of all AEs will be provided by subject. In addition, AEs in the categories above will be provided as listed data. **Between groups assessment** No statistical tests for between-group comparisons will be performed. • The percentages of subjects with solicited local and systemic AEs during the 7 days (including the day of vaccination) following the first (Visit 1), the second (Visit 3) and the third (Visit 4) vaccination for all groups will be calculated. • The percentages of subjects with any unsolicited AEs (including all SAEs) during the 30 days (including the day of vaccination) following the first (Visit 1), the second (Visit 3) and the third (Visit 4) vaccination for all groups will be calculated. • The percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, throughout the study period will be calculated. • The percentages of subjects with AESI throughout the study period will be calculated (for subjects who received rMenB+OMV NZ).

10.3.5. Other analyses

Primary immunogenicity endpoints may be repeated using another panel of strains, if requested.

10.3.6. Interim analyses

All analyses will be conducted on final data and therefore no interim analyses are planned.

10.4. Sequence of analyses

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

11. REFERENCES

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12. APPENDICES

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

12.1.1. List of abbreviations *(Amended 11 October 2022)*

AE:	Adverse Event
AESI:	Adverse Event of Special Interest
CDC:	Centers for Disease Control
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CoP:	Correlate of Protection
COVID-19:	Coronavirus disease 2019
CSR:	Clinical Study Report
DTPa:	Diphtheria, Tetanus and acellular Pertussis
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
FAS:	Full Analysis Set
fHbp:	Factor H binding protein
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMR:	Geometric Mean Ratio
GMT:	Geometric Mean Titer
GSK:	GlaxoSmithKline
hSBA:	Human Serum Bactericidal Assay
IAF:	Informed Assent Form
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonization
IEC:	Independent Ethics Committee
IM:	Intramuscular
IMD:	Invasive meningococcal disease
IRB:	Institutional Review Board

LAR:	Legally Acceptable Representative
LLOQ:	Lower Limit of Quantitation
LOD:	Limit of Detection
LSLV:	Last Subject Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
MenACWY:	Meningococcal serogroups A, C, W, and Y vaccine (*Menveo*)
NadA:	Neisseria Adhesin A
NHBA:	Neisserial Heparin Binding Antigen
OMV:	Outer Membrane Vesicles
PCD:	Primary Completion Date
PI:	Principal Investigator
pIMD:	Potential Immune-Mediated Disease
PorA:	Porin A
rMenB+OMV NZ:	Recombinant Meningococcal B with Outer Membrane Vesicle derived from *Neisseria meningitidis* serogroup B strain NZ98/254 (New Zealand strain) Vaccine (*Bexsero*)
SAE:	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR:	Source data Base for Internet Randomization
SFU:	***Safety Follow-up***
SMP:	Study Management Plan
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual

12.1.2. *Glossary of terms*

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Adverse Event of Special Interest:	Adverse events of special interest (AESIs): are predefined (serious or non-serious) adverse events of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate, because such an event might warrant further investigation in order to characterize and understand it.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 7.3 for details on observer-blinded studies).
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Child in care:	A child who has been placed under the control or protection of an agency, 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 or has an appointed legal guardian.

Combination product:	Combination product comprises any combination of – drug – device – biological product Each drug, device and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) **(Synonym of End of Trial)**	Last subject last visit (LSLV) (Visit X) or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV**.**
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardized term to replace: period, cycle, phase, stage.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 10.2 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, 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 trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Legally acceptable representative: **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
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 adverse events:	Symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.

Pharmacogenomics:	The International Council on Harmonization (ICH) E15 Guidance for Industry defines pharmacogenomics as Study of variation of DNA and RNA characteristics as related to drug or treatment response. Pharmacogenetics, which is a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research are not pharmacogenomics.
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion: date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol'. GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Qualified health care professional:	A licensed or certified health care professional who is permitted by institutional policy to perform protocol required procedures, and who is identified on the Study Staff Signature Log.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.

Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subset (Synonym of Immunosubset):	Selection of blood samples among all blood sample collected at given time point(s) for testing by specific assay

Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

12.1.3. Trademarks

Trademark Information

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

12.2. Appendix 2: Clinical laboratory assays

MenB serum bactericidal assays using human complement (hSBA) - *Bexsero*:

Serum bactericidal activity against rMenB+OMV NZ will be determined by using a validated manual (Tilt-based) hSBA against a standard panel consisting of 4 meningococcal B indicator strains M14459, 96217, NZ98/254 and M07-0241084*. 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 M07-0241084 measures hSBA against the 287 part of the 287-953 antigen, also known as NHBA.

*The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

CCI [redacted]

MenACWY serum bactericidal assays using human complement (hSBA) - *Menveo*:

- 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 a validated hSBA with 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 that has been validated for the 4 MenACWY serogroups 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**.**

MenACWY IgG ELISA

- The anti-MenACWY total IgG antibody (Ab) concentrations will be measured by using a validated Enzyme-Linked Immunosorbent Assay (ELISA) to evaluate the immunogenicity of the capsular polysaccharides of serogroups A, C, W and Y in MenACWY vaccine.
- As per recent recommendation from Authorities, this MenACWY IgG ELISA is under re-validation for the 4 serogroups in alignment with the most recent guidelines and accepted practices on assay validation.
- The assay characteristics (e.g. validated assay cut-offs and units) for each of the serogroup will be determined during the course of the study at the time of the generation of new validated data. Any of these changes will be documented in a protocol amendment or in the clinical study report.

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

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

12.3. Appendix 3: Clinical laboratories

Table 24 GSK Biologicals laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception-B7/44 Rue de l'Institut, 89-B-1330 Rixensart-Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20-B-1300 Wavre-Belgium

Table 25 Outsourced laboratories (potential)

Laboratory	Address
CCI [redacted]	[redacted]
[redacted]	[redacted]

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF) or Informed Assent Form (IAF), 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 amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.

- Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.4.1.1. Responsibilities of the Investigator

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

In addition to what is stated in the Investigator Agreement, the investigator is also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that qualified trained health care professionals (see glossary of terms) are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event (AE) related to the study.
- If permission to do so is given by the subject's parent(s)/LAR(s), ensuring that the subject's primary qualified healthcare provider is informed of the subject's participation in the study.

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

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change,

the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

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

12.4.1.2. Protocol Amendments

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

12.4.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

12.4.3. Informed consent process

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

Subjects must be informed that their participation is voluntary.

Eligible subjects may only be included in the study after providing written informed consent or assent. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or subject's parent(s)/LAR(s) of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must

be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or LAR(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted approximately 2 weeks prior to vaccination on day 1. If the subject and/or LAR(s) is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

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

The content of Informed Consent Form (ICF) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

In accordance with the ICH Harmonized Tripartite Guidelines for GCP, those subjects who can only be enrolled in the study with the consent of the subject's legally acceptable representative (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written IAF. It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by his/her legal representative. It should be assessed whether an assent is required depending of the age of the study population and the local requirements.

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

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

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

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

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

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

12.4.4. Data protection

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

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

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

12.4.5. Publication policy

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

12.4.6. Dissemination of clinical study data

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

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

At the time of study results posting, the full study protocol and SAP will also be posted on Clinicaltrials.gov.

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

If it is not possible to submit a summary of the results within the required timelines in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

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

* As defined in the study protocol.

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12.4.7. Data quality assurance

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

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

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

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

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

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not

obscure the original entry, and should be explained if necessary (e.g. via an audit trail). Safety and rights of subjects must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

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

12.4.8. Source documents

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

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

Definition of what constitutes source data and source documents can be found in the section 12.1.2.

12.4.9. Study and site closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

At study conclusion, the investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

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

12.5.1. Definition of AE

12.5.1.1. AE Definition

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

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

12.5.1.2. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccines 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 vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccines administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).
- Medically attended visits related to adverse events (e.g. Hospital stays, physician visits and emergency room visits).

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

Solicited AEs are derived from organized data collection systems, such as Subject Diaries or interview.

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

12.5.1.3. Events NOT Meeting the AE Definition

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

12.5.2. Definition of SAE

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 subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalization or prolongation of existing hospitalization,

Note: In general, hospitalization signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils 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.

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

d. Results in disability/incapacity, OR

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

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

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

All AEs which do not fall into these categories are defined as non-serious.

It should be noted that a severe AE need not be serious in nature and that a SAE need not, by definition, be severe.

SAEs will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE eCRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine.

12.5.3. Solicited adverse events

The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subjects/parent(s)/LAR(s) for 7 consecutive days (with ongoing solicited AEs collected until resolution or day 30, whichever occurs first), using a pre-defined Subject Diary .

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported in parentheses below:

The collected data will be entered into the Subject eDiary. Please see Section 12.5.8 for more detail.

a. Solicited local (injection-site) adverse events

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

Table 26 Solicited local adverse events*

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

* Solicited local AEs occurring within 30 minutes after vaccination.

b. Solicited systemic adverse events

The following systemic AEs will be solicited:

Table 27 Solicited systemic adverse events

Adolescents (from 11 years of age) and adults
Fatigue
Fever (body temperature ≥ 38.0°C/100.4°F)
Nausea
Headache
Myalgia
Arthralgia

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

The study staff must review the data entered into the Subject Diary as described in Section 12.5.8.

12.5.3.1. Other Solicited Adverse Events

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

The study staff must review the data entered into the Subject Diary as described in Section 12.5.8.

Note: Any solicited adverse event that meets any of the following criteria must be entered into subjects' source document (see Section 12.5.8) and also as an adverse event on the Adverse Event eCRF:

- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see Section 12.5.8.3.3).
- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see Section 12.5.2).

12.5.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subjects/parent(s)/LAR(s) who has signed the informed consent. Please see Section 12.5.3.1 for more detail, where the criteria are listed.

Parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report potential unsolicited AEs that required hospitalization, or emergency room visit, or visit to/by a health care provider that were of concern to the subjects/parent(s)/LAR(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs will be collected during interview with the subjects/parent(s)/LAR(s) and by review of available medical records at the next visit. Unsolicited AEs will be reviewed at the safety follow-up calls as well.

All unsolicited AEs will be collected during the first 30 days after the first (Visit 1), second (Visit 3) and third (Visit 4) injection. Unsolicited AEs leading to vaccine/study withdrawal, medically attended AEs, AESI and SAEs will be collected during the entire study period starting from signature of informed consent until study termination.

12.5.5. Adverse events of special interest (AESIs)

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

12.5.5.1. Arthritis

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

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

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

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

12.5.5.2. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 28. Please refer to section 12.5.9.2 for reporting details.

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

Table 28 List of potential immune-mediated diseases (pIMDs)

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

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

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

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

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

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

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

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

12.5.7.1. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccines but may continue other study procedures at the discretion of the investigator.

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

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

The following should always be considered as SAE and will be reported as described in Sections 12.5.9.1 and 12.5.9.4:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)

  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks' cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccines will be reported to GSK Biologicals as described in Section 12.5.9. While the investigator is not obligated to actively seek this information from former subjects, he/she may learn of a pregnancy through spontaneous reporting.

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

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

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

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

The same individual should preferably complete the Subject eDiary throughout the relevant reporting period.

The subject/subject's parent(s)/LAR(s) should be trained on how to self-measure local solicited adverse events and body temperature.

The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

Subjects/parent(s)/LAR(s) will be instructed to measure and record the body temperature (preferably oral) in the evening. Should additional temperature measurements be performed at other times of day, subjects/parent(s)/LAR(s) will be instructed to record the highest temperature in the Subject eDiary.

Subject eDiary assignment and use:

- Each subject/subject's parent(s)/LAR(s) will be assigned a Subject eDiary and shown how to use the device – this will include how to access the diary, performing test data entry on sample questions, and how to charge and store the device.
- The subject/subject's parent(s)/LAR(s) will self-select a numeric access code secret to themselves. The same individual should preferably make the assessments and complete the Subject eDiary throughout the reporting period (Visit 1-Visit 5).
- The subject/subject's parent(s)/LAR(s) will select an alarm time that suits their daily routines whilst ensuring compliance with protocol requirements.

Subject eDiary instructions must ensure that the subject/subject's parent(s)/LAR(s) understands the following:

- Timely completion of the Subject eDiary on a daily basis is a critical component to study participation.
- The Subject eDiary will allow certain time windows for completion of each day's observations.
- The Subject eDiary employs the use of audio-visual alarms to ensure timely completion of data entry.
- The trained and assigned user of the Subject eDiary must not share access codes with anyone.
- A helpdesk will be provisioned for users of Subject eDiary in case of technical issues, though it must be stressed that the Helpdesk is not a replacement for normal medical care and no medical issues can be discussed with the agents.
- The Subject eDiary itself must never be considered a substitute for direct medical care and any concerns must be communicated to site staff as soon as possible.
  - The subject/parent(s)/LAR(s) will be contacted by the site staff on Days 15, 75, 105, 181, 271, 361, and 451 ***(or Days 15, 75, 105, 181, and 271 for subjects who have not reached Day 271 at the time this amendment takes effect*** via a scripted safety follow-up phone call. At, or in advance of each phone call the site will review the eDiary web-portal for responses entered by the subject/subject's parent/LARs in order to solicit additional information during the phone call e.g. related to unsolicited adverse events, concomitant vaccinations/medication and medically attended events (***Amended 11 October 2022***).
- Any new safety information reported during the safety follow-up phone call or site visits (including a solicited adverse event) cannot be entered into the Subject eDiary. Such information must be described in the source documents as a verbally-reported event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered into the eCRF.

- The subject and/or subject's parent(s)/LAR(s) will bring the eDiary at each visit. The eDiary will be collected by site staff at Day 121 (Visit 5).

Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30 minute post-vaccination period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary.

The Investigator or delegated staff should monitor the Subject's Diary status throughout the study for compliance and any solicited local and systemic adverse events that were of concern to the subject.

- No corrections or additions of data recorded by the subjects/parent(s)/LAR(s) will be allowed once diary completion for that day has been performed.
- The Subject Diary will be designed in such a way as to prevent any blank, incomplete or biologically implausible entries. Subjects/parent(s)/LAR(s) will be instructed to fully complete the Subject Diary each day, as per the instructions provided.
- At or just in advance of each subject visit, site staff must review the Subject Diary data via the provider's web portal. It is necessary for site staff to acknowledge in the source documents that review of Subject Diary data for the preceding post-vaccination period has been performed. At the end of the study it is necessary for the investigator to acknowledge in the eCRF that the review of Subject Diary data has been performed for each subject.
- For vaccination visits, site staff must ensure that each subject's Diary is prepared for data capture in the ensuing post-vaccination period by confirming the visit within the eDiary/eDiary system.
- Any new safety information reported during the site visit (including a solicited reaction) cannot be entered into the Subject Diary. Such information must be described in the source notes as a verbally-reported event. Any adverse reaction reported in this fashion must be described as an unsolicited reaction and therefore entered on the adverse event page of the eCRF.

12.5.8.1. Post-vaccination reminders

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

12.5.8.1.1. Subject Diary Alerts

The subject/subject's parent(s)/LAR(s) will receive daily reminders via the Subject Diary device's in-built audio-visual alarms to alert the user to complete the diary during the post vaccination period, which is from Day 1 though Day 7, after each vaccination visit.

The Subject Diary system will also allow for regular alerts to be issued via email to site staff indicating where subjects may need to be contacted due to:

- Non-compliance (i.e. failing to enter or transmit diary data),
- Reporting of any severe solicited reactions,
- Subject experienced an unsolicited adverse event that required hospitalization or visit to the emergency room or medically attended events that were of concern to the parents/LAR(s).

Sites must assess these alerts when received and contact subjects as necessary. Please refer to Section 5.3 on the premature withdrawals from the study and Section 12.5.8.3 on the evaluation of Adverse Events for guidance on necessary action in the event of one of these alerts.

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

All AEs during 30 days following administration of each dose of study vaccines must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Any solicited AE that has not resolved within 30 days post vaccination and is reported during clinic visits or safety follow-up calls will be entered into the subject's eCRF as an unsolicited AE. It will also be included in the subject's source documents at the site by the investigator/site staff as a verbally reported event. It will not be included in the Subject eDiary. These AEs will be analysed as unsolicited AEs (i.e. in the Unsolicited Safety Set).

The time period for collecting and recording SAEs will begin at the first receipt of study vaccines and will end 12 months following administration of the last dose of study vaccines for each subject. See Section 12.5.9 for instructions on reporting of SAEs. However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK Biologicals product will be recorded from the time a subject consent to participate in the study.

All AEs occurring after the ICF is signed but prior to receiving study vaccine will be documented as an AE and recorded within source document and eCRF. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from "treatment emergent" AEs (AEs occurring after administration of the first study vaccine). All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccines until study end.

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

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccines and will end 12 months following administration of the last dose of study vaccines. See section 12.5.9 for instructions on reporting of pregnancies.

The time period for collecting and recording of AESIs will begin at the first receipt of study vaccines and will end 12 months following administration of the last dose of study vaccines. See section 12.5.9.5 for instructions on reporting of AESIs.

12.5.8.3. Evaluation of adverse events and serious adverse events

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

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

'*Have you felt different in any way since receiving the vaccines or since the previous visit?*' (for subjects above 18 years of age)

OR

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

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

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

12.5.8.3.2. Assessment of adverse events

1. Assessment of intensity

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

Table 29 Intensity scales for solicited symptoms in adults and children of 6 years of age or more

Adolescents (from 11 years of age) and adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Injection Site Induration, Swelling, Erythema	0	1 – 24 mm
	1	25 - 50 mm
	2	51 - 100 mm
	3	>100 mm
Temperature*	0	< 38.0°C (100.4°F)
	1	≥ 38.0 - 38.9°C (100.4 – 102.02°F)
	2	≥ 39.0 - 39.9°C (102.2 – 103.82°F)
	3	≥ 40.0°C (104.0°F)
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
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
Generalized Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Generalized Arthralgia	0	Normal
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

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

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

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

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

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

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

2. Assessment of causality

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

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

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

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

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

If an event meets the criteria to be determined as 'serious' (see Section 12.5.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

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

AEs will also be evaluated by the investigator for the co-existence of any of the other following conditions:

"Medically attended AEs": an AE that leads to a visit to a healthcare provider.

AEs leading to withdrawal: AEs leading to study or vaccine withdrawal.

If solicited or unsolicited AEs have been reported and the subject and/or parent(s)/LAR(s) indicated that the symptoms required medical attendance or were of concern, the subject and/or parent(s)/LAR(s) must be contacted for further information.

When the subject and/or parent(s)/LAR(s) is contacted for any of these reasons, the contact must be documented in the subject's source documentation.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine(s) or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing AEs at the time of each subject's last visit should be documented in the subject's medical chart.

The end date of AEs ongoing at the time of each subject's last visit and judged by the investigator as not chronic or stable should be documented in the source documents.

3. Assessment of outcomes

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

- Recovered/resolved.
- Recovering/resolving.

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

12.5.8.3.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject/subject's parent(s)/LAR(s) will be asked if the subject 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.

12.5.8.4. Recording of AEs related to COVID-19

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

- Suspected COVID-19 case
- Probable COVID-19 case
- Confirmed COVID-19 case

If subject is diagnosed with COVID-19 as above, report each occurrence in the COVID-19 Coronavirus Infection Assessment form. In addition, complete for each occurrence as AE on the Non-Serious Adverse form or as SAE on the Expedited Adverse Event Report form (depending on the level of seriousness as assessed by the Principal Investigator or delegate). Please also report the relevant medications related to this event. Follow the guidelines applicable for those forms on how to record COVID-19.

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

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

SAEs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pregnancy.

AESIs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a AESIs.

12.5.9.2. SAEs requiring expedited reporting to GSK Biologicals

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

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

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

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

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

12.5.9.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report within 24 hours.

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

12.5.9.5. Reporting of AESI's to GSK Biologicals

Once an AESI is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows specify that the event is an AESI and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the AESIs standard questionnaire provided. Even if the investigator does not have all information regarding an AESI, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

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

Refer to Section 12.5.9.3 for back-up system in case the electronic reporting system does not work.

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

When additional SAE, pregnancy, or AESI information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 17.

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

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

12.5.11.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 17).

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

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

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

The investigator will follow subjects:

- with SAEs, AESIs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- with other non-serious AEs, until one year after LSLV or if the subject is lost to follow-up.

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

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

12.5.11.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the paper pregnancy follow-up report/electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

The following should always be considered as SAE.

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

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

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

12.6.1. Definitions

12.6.1.1. Woman of Childbearing Potential (WOCBP)

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

12.6.1.1.1. Women in the following categories are not considered WOCBP

- Premenarchal

Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

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

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

- Postmenopausal female

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

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

12.6.2. Contraception guidance

- Female subjects of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in GSK list of highly effective contraceptive methods as described in Table 30.

Table 30 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulationb • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • 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 WOCBP 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 subject's entry into the study, and this male is the sole partner for that subject, *(The information on the male sterility can come from the site personnel's review of the subject's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

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

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilised during the treatment period and for at least 2 months after the last dose of study treatment.

12.6.3. Collection of pregnancy information

12.6.3.1. Female Subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in 12.5.9. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

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

12.7. Appendix 7: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

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

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether 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 an AE related to the use of a medical device. This definition includes any AE resulting from:
  - insufficient or inadequate instructions for use (i.e. user error), or
  - any malfunction of a medical device, or
  - intentional misuse of the medical device.

12.7.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
c. Led to death
d. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
e. Led to fetal distress, fetal death or a congenital abnormality or birth defect
f. Is a suspected transmission of any infectious agent via a medicinal product
Serious Adverse Device Effect (SADE) definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 3.3).

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

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- E-mail/Facsimile transmission of the paper 'Medical device or combination product with device deficiency/incident report form' is the preferred method to transmit this information to the sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of 'Medical device or combination product with device deficiency/incident report form' sent by overnight mail or courier service.
- Contacts for reporting can be found in Section 8.4.6.1.
- GSK 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.

12.8. Appendix 8: Protocol Amendment History

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

DOCUMENT HISTORY	
Document	Date of Issue
Amendment 7	11 October 2022
Amendment 6	21 June 2022
Amendment 5	13 April 2021
Amendment 4	26 November 2020
Amendment 3	29 September 2020
Amendment 2	23 January 2020
Amendment 1	14 August 2019
Original Protocol	28 June 2016

Overall Rationale for the Amendments:

Section # and Name	Description of Change	Brief Rationale
Amendment 7:		
Contributing authors	Updated job titles	Internal update in name of job titles
Sponsor signatory page	Updated job title	Internal update in name of job title
Section 1	Updated objectives and endpoints table Updated overall design figure Updated text	To incorporate 2 additional primary endpoints To incorporate a shortened safety follow-up into the overall design figure To introduce a shortened safety follow-up period in subjects who have not reached safety follow-up (SFU) 5 (Day 271) at the time this amendment takes effect
Table 3	Added a bullet mark for study conclusion also under SFU 5 and added a footnote with details	To introduce a shortened safety follow-up period in subjects who have not reached SFU 5 (Day 271) at the time this amendment takes effect
Table 4	Updated	To extend the visit window to 28 days post reference day
Table 5	Addition of footnote	To introduce a shortened safety follow-up period in subjects who have not reached SFU 5 (Day 271) at the time this amendment takes effect
Table 6	Updated	To incorporate 2 additional primary endpoints
Figure 1	Updated	To introduce a shortened safety follow-up period in subjects who have not reached SFU 5 (Day 271) at the time this amendment takes effect

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Section 5.4 Section 7.5.1 Section 8.4.3 Section 8.6 Section 12.5.8	Addition of text	To introduce a shortened safety follow-up period in subjects who have not reached SFU 5 (Day 271) at the time this amendment takes effect
Table 14	Table revised	To provide clarity on what assay to be performed at which visit.
Table 15	Table title edited	To clarify that study conclusion at Day 451 is applicable in subjects who have crossed Day 271
Table 16	New table created	To clarify that study conclusion at Day 271 is applicable in subjects who have not reached Day 271
Amendment 6:		
Contributing authors	Names of CEPL, CRDL, SDL, LDL, ODM, CTSM, Safety Scientist, Statistician, Lead Statistician, GRA and Global patent representative updated.	Change in study team members.
Sponsor signatory page	Name of sponsor signatory updated	Change in study team members.
Table 3	Addition of footnote	To clarify that the recording of SAEs related to study participation starts from the signature of the ICF.
Section 5.2 Section 12.1.2	Definition of End of Study updated.	This update in definition accounts for instances where LSLV precedes the last date of testing/reading released of the human biological samples or imaging data.
Section 6.2.1	Deletion of the exclusion criterion about obesity.	Both *Bexsero* and *Menveo* are already licensed in both the US and Italy, neither product labels list individuals with obesity as a contraindication.
Section 6.2.2	Addition of MenQuadfi to the list of quadrivalent Meningococcal vaccines	MenQuadfi was approved in the US in 2021
Section 8.3.2.1	Addition of the word ‘any’ in from of vaccination.	To clarify that sample collection for immunogenicity assessments should be done prior to any vaccination.
Table 15	Addition of medically attended AEs Addition of footnote	To clarify that safety information on medically attended AEs is also collected. To clarify that the recording of SAEs related to study participation starts from the signature of the ICF.
Section 11	References updated	Alignment of COVID-19 reporting requirement to the local guidelines
Table 16 Section 12.5.9.4 Section 12.6.3.1	Modification of timeframe to report pregnancies 2 weeks to 24 hours	To align with industry standards for reporting pregnancies.
Section 12.1.1:	Addition of LSLV	LSLV features in the body of the document
Section 12.5.8.4	Addition of wording on recording of AEs related to COVID-19	Alignment of COVID-19 reporting requirement to the local guidelines
Section 12.5.8.4.1	Deletion of WHO Case Definition	Alignment of COVID-19 reporting requirement to the local guidelines
Amendment 5:		
Co-ordinating author(s)	Name of science writers updated.	Change in study team members.

Section # and Name	Description of Change	Brief Rationale
Contributing authors	Name of LDL updated.	Change in study team members
Sponsor signatory page and investigator agreement page	Addition of note on alternative signature process. Addition of bullet point.	Update in the protocol template instructions.
Section 1 Table 6 Table 13 Table 14 Section 10.3.3 Section 12.2	Footnote and text updated.	Clarification that reporting of changes to the NHBA strain during the study will be documented in the clinical study report.
Table 3	Modification of ICF signature window.	Team agreement to provide a wider window to increase operational feasibility.
Section 6.3	Addition of wording on emergency mass vaccination.	Update in the protocol template wording.
Table 9	Addition of new row “Product Category’.	Update in the protocol template instructions to define the product category of each study intervention administered in the study:
Section 7.3.1	Explanatory text added to provide the criteria for emergency unblinding.	Text included to follow-up on a specific question raised by AIFA Health Authority on 08 January 2021
Table 13	CCI [redacted]	[redacted]
Table 14	Deletion of column: Components priority rank.	Simplification of the serological section.
Table 15	Addition of footnote	Clarification on how solicited AEs that continue beyond day 7 after vaccination will be handled.
Section 8.4.7	Addition of new section on medical device deficiencies.	Update in the protocol template wording.
Section 10.1.1.1	Removal of order of statistical testing of the strains.	Simplification of the statistical strategy.
Section 10.1.2	Removal of order of statistical testing of the strains.	Simplification of the statistical strategy.
Section 12.1.2	Addition of two new terms in glossary of terms.	Update in the protocol template wording.
Section 12.2	Removal of reference to Axiolab Image analysis System	Use of alternative equipment planned
Table 23	CCI [redacted]	[redacted]
Table 24	CCI [redacted]	[redacted]
Section 12.4.3	Modification of ICF signature window.	Team agreement to provide a wider window to increase operational feasibility.
Section 12.5.3	Addition of text.	Clarification on how solicited AEs that continue beyond day 7 after vaccination will be handled.
Section 12.5.3.1	Deletion of bullet point.	The deleted bullet point was incorrect.
Section 12.5.5.1	Additional text added to ‘threshold of duration of 6 weeks.	This is to clarify that threshold of duration pertains to signs/symptoms of arthritis.
Section 12.5.8.2	Addition of paragraph.	Clarification on how solicited AEs that continue beyond day 7 after vaccination will be handled.

Section # and Name	Description of Change	Brief Rationale
Section 12.7	Addition of new appendix.	Update in the protocol template to cover FDA requirement for medical device deficiencies reporting.
Amendment 4:		
Contributing authors	Name of CRDL Name of CTSM	Change in study team members
Sponsor signatory page and investigator agreement page	Short title replaced by Title. No change in the wording	Change in the protocol template instructions
A note in Table 3 under laboratory assay	Deletion of Visit 2 from the note	Incorrect sentence, no vaccine administration on Visit 2.
CCI [redacted]		
Section 8.3.2.1	Additional text added to clarify the clinical circumstances that may warrant delay in blood sample collection for immunogenicity assessments	Use of antibiotics may alter the immunogenicity assessments
Section 10.1.2	Correction of treatment group names for the secondary objective, hypothesis 3, under *the standard deviations for hSBA titer* paragraph	Typographical error
Section 12.1.1	Addition of 2 abbreviations	Additional texts in the body of document
Section 12.2	Updated text under clinical laboratory assays for new hSBA for *Menveo*	Update in the status of the laboratory assay
Section 12.4.2	Updated text for the financial disclosure description	Update in the protocol template wording
Section 12.4.7	Text on quality tolerance limits (QTL) was added	Update in the protocol template wording
Amendment 3:		
Co-ordinating author(s)	Name of science writer updated	Change in study team members
Contributing authors	Names of CEPL, ODM, CTSM, CLS and Safety representatives updated.	Change in study team members
Table 3 Schedule of Activities	Reference section updated for symptom-directed physical examination. Footnote * added regarding recording of COVID-19 infection related AEs and SAEs.	Symptom-directed physical examination is now described only in Section 8.2.4. COVID-19 infection-related AEs/SAEs to be also recorded in a separate eCRF page.
Table 3 Schedule of Activities	Visit window row deleted and reference to Table 4 and Table 5 included.	A separate table for intervals between visits and telephone contacts has been added.
Table 5 Intervals between study visits and safety follow-up calls	A separate table for intervals between visits and telephone contacts has been added.	Table added to clarify the windows for safety follow-up (SFU) calls are in relation to previous visit..
Section 5.2 Overall design	Primary Completed Date updated	Data collected at Month 15 (Day 451) is part of the primary outcome. Hence PCD date was updated as Study termination-call Day 451.
Section 6.3 Criteria for temporary delay for enrolment, vaccination and/or blood sampling	Criteria for temporary delay for enrolment, vaccination and/or blood sampling due to COVID-19 were added	Criteria added to clarify temporary delay for enrolment, vaccination and/or blood sampling procedures due to COVID-19
Table 9 Treatments administered	Entry for *Menveo* and *Bexsero* was updated and a footnote was added.	Change in the formulation description and presentation description was done to align

Section # and Name	Description of Change	Brief Rationale
	Entry for placebo volume was updated and a footnote was added.	with the internal vaccine database dictionary. CCI [redacted] Change in placebo volume from 0.5 mL to 0.65 mL to be aligned with the certificate of analysis. A footnote was added in order to avoid future amendments if the placebo volume were to vary in different batches and also to clarify that the volume of the pre-filled syringe administered will be within a range and the full volume should be injected.
Table 10 Administration and Laterality	A footnote was added.	Laterality defined due to multiple vaccinations at different visits.
Section 7.3.1 Emergency unblinding – Table 11 Contact information for emergency unblinding	US and Italy toll-free numbers updated. Reference added to SPM for individual country numbers.	Helpdesk numbers have been updated.
Section 8.1	Section updated	Paragraph added for special circumstances such as COVID-19.
Section 8.2.3 Medical history	Section updated	Description on physical examination was deleted
Section 8.2.4 Physical examination	Section updated	Description on physical examination in Section 8.2.3 was moved to Section 8.2.4
Section 8.3 Efficacy assessments	Section updated	The wording “future research” was updated as “further research” to align to the most recent GSK protocol and ICF template wording.
Table 15 Reporting periods for collecting safety information	Footnote added	A footnote was added to clarify including COVID-19 infection related AEs will be collected.
Section 8.7 Study procedures during special circumstances	Section added.	Certain study procedures can be adapted during special circumstances such as COVID-19 pandemic.
Section 11 References	Section updated	2 new references were added
Section 12.1.1 List of abbreviations	List updated	List was updated to include COVID-19 expansion.
Section 12.5.8 Detecting and recording adverse events, serious adverse events and pregnancies	When a person other than the subject/subject’s parent(s)/LAR(s) helps in the completion of the eDiary, their identity must be documented in the subject’s source record and not in the subject diary.	As there is no option available to enter a name in eDiary, it was agreed to include the instruction for training and capturing individual’s information in source document.
Section 12.5.8.4	Section added	Section added to include recording of AEs related to COVID-19.
Section 12.5.8.4.1	Section added	Section added to describe WHO case definitions for COVID-19.
Amendment 2:		
Scientific rationale for Inclusion criteria (Section 6.1)	Modified the inclusion criteria for subject selection. Subjects enrolled will be required to have received a priming dose of MenACWY, *Menveo or Menactra* at	The inclusion of a booster recommendation in *Menveo*’s US Prescription Insert, with the recommendation to administer the booster at least 4 years after the priming dose, has only been approved by US FDA in

Section # and Name	Description of Change	Brief Rationale
	least 4 years prior to informed consent, instead of 3 years prior.	December 2019. As a result, the company intends to align the inclusion criterion in the V72_79 study with the recently introduced booster recommendation in the US, and amend the protocol accordingly to allow inclusion of subjects who have received a meningococcal ACWY vaccine 4 years or greater in the past.
Amendment 1		
Across the document	Assay validations have been updated: • Develop, validate, and use a new "agar overlay" serum bactericidal assay using human complement (hSBA) and automated colony counting method in order to quantify serogroup-specific immunogenicity of the MenACWY vaccine against *N. meningitidis* serogroups A, C, W and Y (MenACWY agar-overlay hSBA); • Validate the MenB manual (Tilt) hSBA for the use of the M14459 (fHbp), 96217(NadA) NZ98/254 (PorA) and M07-0241084 (NHBA) indicator strains to measure immunogenicity of *Bexsero* against *N. meningitidis* serogroup B. • Modification of the 4-fold increase in post-vaccination hSBA titer definition when the pre-vaccination titer is below the limit of detection. • Modification of the population set to be used for safety analysis; exposed set is to be used for all safety analyses.	To support the primary endpoint analyses of this study and based on the most recent expectations set by Center for Biologics Evaluation & Research (CBER) recommendation.

Detailed description of Protocol Amendment 7:

Additional texts are presented in bold italics and deleted texts are presented in strikethrough.

- Title page: Contributing authors
  - PPD ***Clinical Sciences Lead*** ~~Clinical Research and Development Lead~~
  - PPD, Local Delivery Lead
  - ~~PPD SERM Safety Scientist~~
  - PPD
  - PPD, ***SERM Principal Scientist***

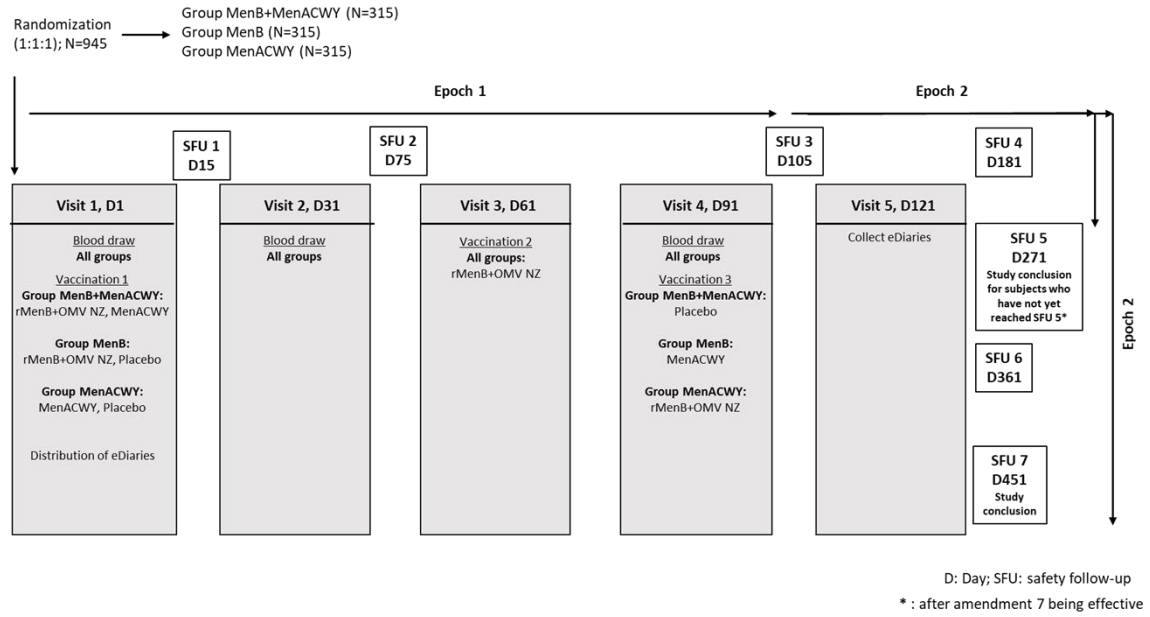
– PPD , ***Clinical Project Lead*** ~~Clinical and Epidemiology Project Leader (CEPL)~~from Protocol Amendment 3 onwards and PPD , ***Associate Clinical Project Lead*** ~~Associate Clinical and Epidemiology Project Leader (CEPL)~~ from Protocol Amendment 6 onwards

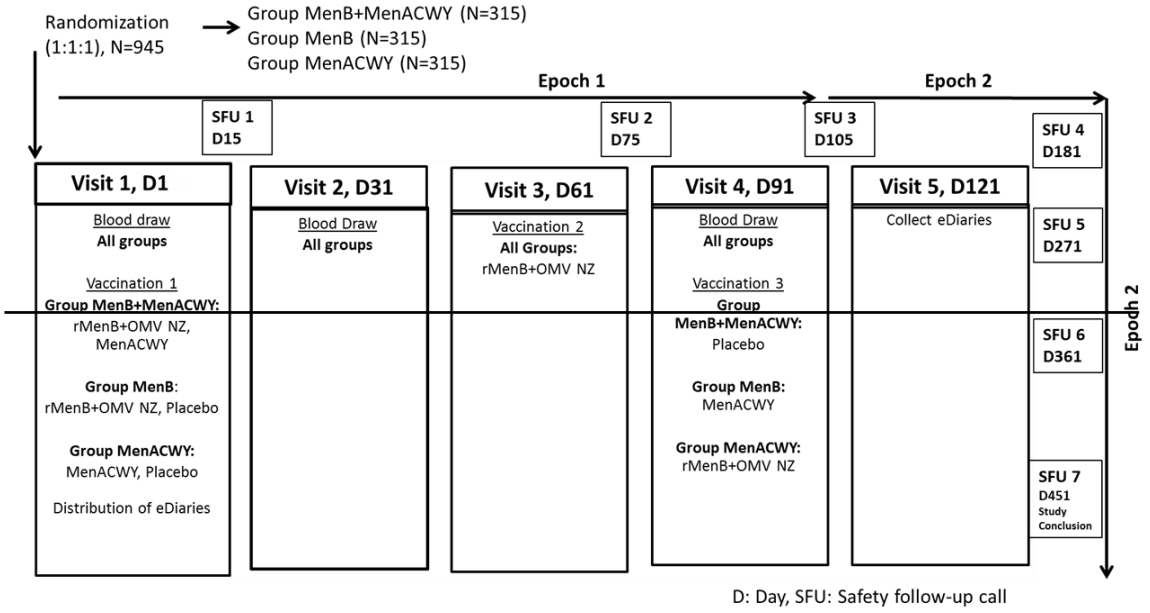
- Protocol amendment & Sponsor signatory page: Sponsor signatory – Alessandro Ble, ***Director, Associate Clinical Project Lead*** ~~Associate Clinical and Epidemiology Project Lead~~

- Section 1: Synopsis

Objectives	Endpoints
Primary	
To assess the safety and tolerability of rMenB+OMV NZ and MenACWY, when administered concomitantly or alone, in healthy subjects 16-18 years of age.	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 30 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, throughout the study period (Day 1/Month 0 to Month **9**~~15~~). • The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI throughout the study period (Day 1/Month 0 to Month **9**~~15~~). • ***Among subjects who are followed for 12 months after their last dose:*** ○ ***The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, between SFU 5/Month 9 and SFU 7/Month 15.*** ○ ***The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI between SFU 5/Month 9 and SFU 7/Month 15.***

Overall design:





Duration of the study:

Epoch 002: Safety follow-up period starting at Visit 4 (Day 91) and ending at Study termination-call (Day 451 [Month 15]) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 at the time this amendment takes effect.***

- Table 3: Schedule of Activities

Study Conclusion¥										●		●	See Section 5.4 for more information.

Footnote: ***¥ Safety follow up and contact will terminate at SFU 5 for subjects who have not reached SFU 5 at the time this amendment takes effect. Please note that for these subjects, the termination call would be performed at SFU 5.***

- Table 4: Intervals between study visits

Interval	Length of interval	Allowed interval
Visit 1 → Visit 2	30 days	23 - ***58*** ~~51~~days
Visit 1 → Visit 3	60 days	53 - ***88*** ~~81~~days
Visit 3 → Visit 4	30 days	23 - ***58*** ~~51~~days
Visit 4 → Visit 5	30 days	23 - ***58*** ~~51~~days

- Table 5: Intervals between study visits and safety follow-up calls

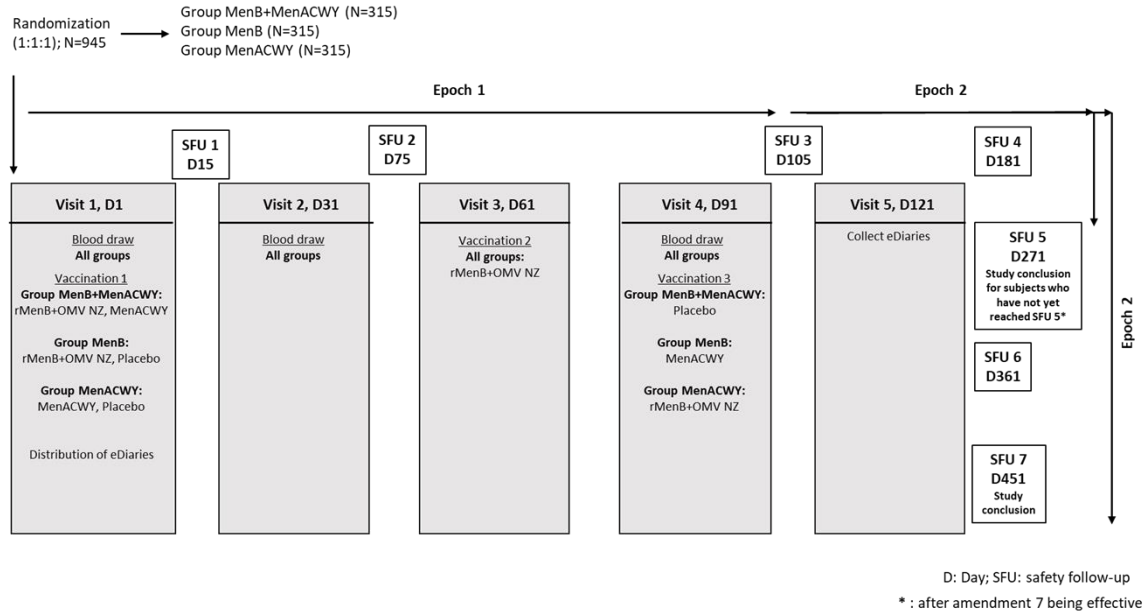
Footnote: ****Safety follow up will terminate at SFU 5 for subjects who have not reached SFU 5 at the time this amendment takes effect.***

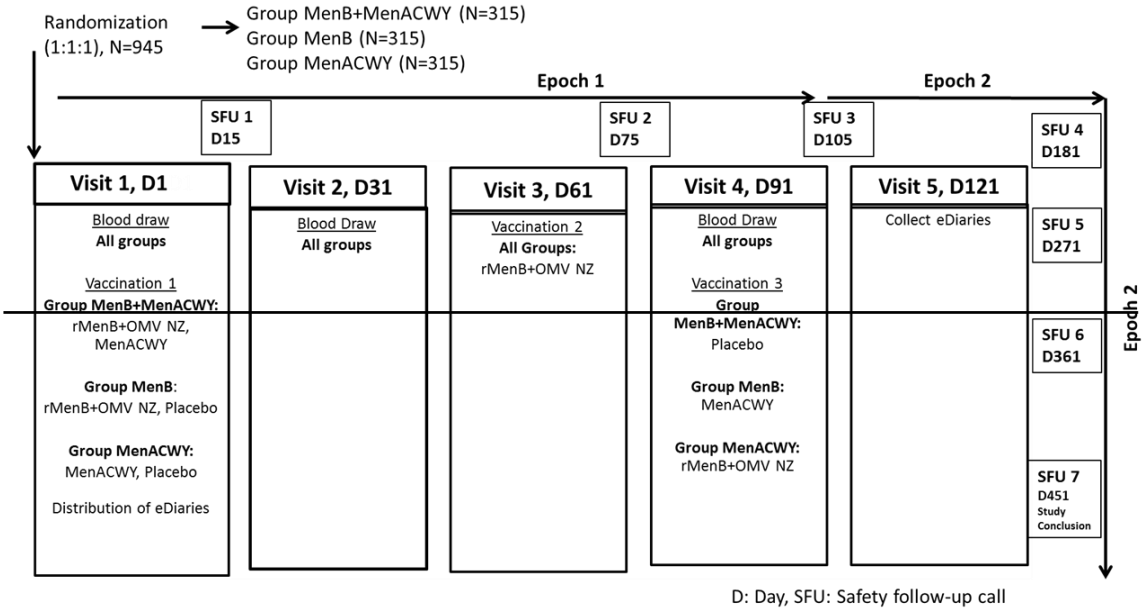
- Table 6: Study objectives and endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of rMenB+OMV NZ and MenACWY, when administered concomitantly or alone, in healthy subjects 16-18 years of age.	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs), AEs leading to withdrawal and medically attended AEs during the 30 days (including the day of vaccination) following the first (Visit 1, Day 1/Month 0), the second (Visit 3, Month 2) and the third (Visit 4, Month 3) vaccination for all groups. • The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal, and medically attended AEs, throughout the study period (Day 1/Month 0 to Month ***9***~~15~~). • The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI throughout the study period (Day 1/Month 0 to Month ***9***~~15~~). • ***Among subjects who are followed for 12 months after their last dose:*** ○ ***The frequencies and percentages of subjects with SAEs, AEs leading to***

Objectives	Endpoints
	withdrawal, between SFU 5/Month 9 and SFU 7/Month 15. ○ ***The frequencies and percentages of subjects (who received rMenB+OMV NZ) with AESI between SFU 5/Month 9 and SFU 7/Month 15.***

- Figure 1: Study design overview





- Section 5.2.1: Overall design

  – Epoch 002: Safety follow-up period starting at Visit 4 (Day 91) and ending at Study termination-call (Day 451 [Month 15]) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 at the time this amendment takes effect.***

- Primary completion Date (PCD): Study termination-call (Day 451) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 at the time this amendment takes effect.***
- End of Study (EoS): Last subject last visit (LSLV) [last concluding contact on Day 451 ***(Month 15) or Day 271 (Month 9) for subjects who have not reached Day 271 at the time this amendment takes effect*** or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV

- Section 7.5.1: Recording of concomitant medications/products and concomitant vaccinations

  Relevant medications/products administered during the period (Day 1 to Day 451) ***or (Day 271) for subjects who have not reached Day 271 at the time this amendment takes effect.***

  Any concomitant vaccination administered in the period starting 14 days before the first dose of study vaccines and ending at the last study contact (Day -14 to Day 451) ***or (Day 271) for subjects who have not reached Day 271 at the time this amendment takes effect.***

- Table 14: Immunological read-outs

Blood sampling timepoint		**Subset/Sub-cohort Name**	**No. of subjects**	**Component**
Type of contact and timepoint	**Sampling timepoint**			
Visit 1 (Day 1)	Pre-Vacc	***Group MenB+MenACWY***	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084**** ***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY***
		Group MenB	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****
		Group MenACWY	***315***	***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY***
Visit 2 (Day 31)	Post Vacc1	***Group MenB+MenACWY***	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084**** ***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY*** ***ELISA IgG anti meningococcal A, C, W, Y***

		Group MenB	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****
		Group MenACWY	***315***	***hSBA-MenA*** ***hSBA-MenC*** ***hSBA-MenW*** ***hSBA-MenY*** ***ELISA IgG anti meningococcal A, C, W, Y***
Visit 4 (Day 91)	Post Vacc2	***Group MenB+MenACWY***	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****
		Group MenB	***315***	***hSBA-M14459*** ***hSBA-96217*** ***hSBA-NZ98/254*** ***hSBA-M07-0241084****

*The NHBA indicator strain M07-0241084 may be subject to change during the study before clinical testing starts. In this case, this change will be documented in the clinical report.

- Section 8.4.3: Safety Follow-up calls

  A total of seven safety follow-up calls will be performed. Safety follow-up calls will be performed on Day 15, Day 75, Day 105, Day 181, Day 271, Day 361 and Day 451 (study termination). ***For subjects who have not reached Day 271 at the time this amendment takes effect, a total of 5 safety follow-up calls will be performed. Safety follow-up calls will be performed on Day 15, Day 75, Day 105, Day 181, and Day 271 (study termination).***

- Table 15: Reporting periods for collecting safety information ***in subjects who have crossed D271***

- ***Table 16: Reporting periods for collecting safety information in subjects who have crossed D271***

• ***Event***	***V1***		***V2***	***V3***		***V4***		***V5***			***Study Conclusion***
	D1	***D15***	***D31***	***D61***	***D75***	***D 91***	***D105***	***D121***	***D181***		***D271***
Solicited local and systemic AEs*											
Unsolicited AEs within 30 days post-vaccination											
Medically attended AEs, AEs/SAEs leading to withdrawal from the study*											

SAEs	
SAEs related to the study vaccines	
SAEs related to study participation or concurrent GSK medication/vaccine¥	
Pregnancies	
AESIs/pIMDs	

AE: Adverse event, AESI: adverse event of special interest, D: Day, SAE: Serious adverse event, V: Visit.
****Solicited AEs to be collected for 7 days following each vaccination, with ongoing solicited AEs collected until resolution or day 30, whichever occurs first.***
***** Including COVID-19 infection related AEs.***
¥Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a parent(s)/LAR(s) or participant signs the consent form to the end of the study

- Section 8.6: Study conclusion

  The study termination call will occur on study Day 451 (after safety follow up call 7) ***or (Day 271 [Month 9]) for subjects who have not reached Day 271 [Month 9] at the time this amendment takes effect.*** The termination visit will be a phone call.

- Section 12.1.1: List of abbreviations

SFU	***Safety Follow-up***

- Section 12.5.8: Detecting and recording adverse events, serious adverse events and pregnancies

  The subject/parent(s)/LAR(s) will be contacted by the site staff on Days 15, 75, 105, 181, 271, 361, and 451 ***(or (Day 271) for subjects who have not reached Day 271 at the time this amendment takes effect*** via a scripted safety follow-up phone call.

Detailed description of Protocol Amendment 6:

Additional texts are presented in bold italics and deleted texts are presented in strikethrough.

- Title page: Contributing authors

- PPD [redacted], Clinical Research and Development Lead
- PPD [redacted], Study Delivery Lead
- PPD [redacted], Local Delivery Lead
- PPD [redacted], Oversight Data Manager
- PPD [redacted], Clinical Trials Supply Manager
- PPD [redacted], SERM Safety Scientist
- PPD [redacted], Global Regulatory Affairs
- PPD [redacted], Global Patent
- PPD [redacted], Study Statistician
- PPD [redacted], Lead Statistician
- PPD [redacted], Clinical and Epidemiology Project Leader (CEPL) from Protocol Amendment 3 onwards and PPD [redacted], ***Associate Clinical and Epidemiology Project Leader (CEPL) from Protocol Amendment 6 onwards.***

- Protocol amendment 6 Sponsor signatory page: Sponsor signatory – ***Alessandro Ble***, Associate Clinical and Epidemiology Project Lead
- Table 3: Schedule of Activities

*Footnote:*** ***Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a parent(s)/LAR(s) or participant signs the consent form to the end of the study***

- Section 5.2: Overall design

  End of Study (EoS): ***Last subject last visit (LSLV) (last concluding contact on Day 451) or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV*** ~~the date of release of the last testing results, to be achieved not later than 8 months after LSLV~~.

- Section 6.2.1: Medical conditions

  ~~Are obese at screening (obesity is defined as a BMI of ≥ 95th percentile for age and gender).~~

- Section 6.2.2: Prior/Concomitant therapy

  Previous vaccination with two doses of quadrivalent meningococcal conjugate vaccine (MenACWY, *Menveo, Menactra* ***or MenQuadfi***)

- Section 8.3.2.1: Blood sampling for immunogenicity response assessments

  In clinic visits where a blood draw and a vaccination are planned, ensure that all samples collected for immunogenicity assessments are taken prior to ***any*** vaccination

- Table 15: Reporting periods for collecting safety information

Medically attended AEs, AEs/SAEs leading to withdrawal from the study**	

Footnote: ***¥Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a parent(s)/LAR(s) or participant signs the consent form to the end of the study***

- Table16 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

Pregnancies	***24 hours*** ~~2 weeks~~*	electronic pregnancy report	***24 hours*** ~~2 weeks~~ *	paper pregnancy follow-up report/electronic pregnancy report

- Section 11: References

  World Health Organization (WHO). Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance. WHO, 2019 [cited 11-SEP-2019] Available from: https://www.who.int/publications/i/item/10665-331501

  World Health Organization (WHO). WHO COVID-19 Case Definition. WHO, 2020 [cited 11-SEP-2019] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1

- Section 12.1.1: List of abbreviations

LSLV	***Last Subject Last Visit***

- Section 12.1.2: Glossary of terms

End of Study (EoS) **(Synonym of End of Trial)*:***	***Last subject last visit (LSLV) (Visit X) or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.*** ~~For studies with collection of human biological samples and/or imaging data, the End of Study is defined as follows: Last subject last visit (last concluding contact on Day 451) or Last testing results released of samples collected at Visit 4*~~ ~~* In this case EoS must be achieved no later than 8 months after LSLV (last concluding contact).~~

- Section 12.5.8.4: Recording of AEs related to COVID-19

  For COVID-19 infection-related AEs, sites should follow routine AE/SAE processes as outlined in the protocol, using the following terms according to ***the latest COVID-19*** ~~WHO defined~~ case definitions ***criteria in effect at the institution***

  - Suspected COVID-19 case

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

- Section 12.5.8.4.1: ~~WHO Case Definition~~

  ~~Suspected COVID-19 case~~

  ~~A. A person who meets the clinical AND epidemiological criteria~~

  ~~Clinical criteria:~~

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

  ~~AND~~

  ~~Epidemiological criteria:~~

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

  ~~OR~~

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

- ~~Probable COVID-19 case~~

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

  ~~OR~~

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

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

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

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

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

  ~~OR~~

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

~~OR~~

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

- ~~Confirmed COVID-19 case~~

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

- Section 12.5.9.4: Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report ~~WITHIN 2 WEEKS~~within ***24 hours***.

Section 12.6.3.1: Female subjects who become pregnant

Information will be recorded on the appropriate form and submitted to GSK within ~~2 weeks~~***24 hours*** of learning of a subject's pregnancy

Detailed description of Protocol Amendment 5:

Additional texts are presented in bold italics and deleted texts are presented in strikethrough.

- Title page: Contributing author – PPD , Scientific Writing
- Title page: Contributing authors – PPD , Local Delivery Lead
- Protocol amendment 5 Sponsor signatory page:

  Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.
- Protocol amendment 5 Investigator agreement:

  That I will comply with the terms of the site agreement.
- Section 1: Synopsis

  Footnote: ****The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report****.*
- Table 3: Schedule of Activities

Informed consent	●												Activities that can be performed at a separate visit before Visit 1 (***approximately 2 weeks*** ~~maximum 5 days~~ before the Visit 1). AEs / SAEs related to study participation or to a concurrent GSK medication/vaccine should also be recorded starting from this separate visit. Inclusion/exclusion criteria should be re-checked prior to vaccination at visit 1. See Section 12.4.3 for details.

- Table 6: Study objectives and endpoints

  Footnote: ****The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report****.*
- Table 9: Treatments administered

Product Category	***Combination Product***	***Biological Product***	***Combination Product***

- Section 6.3: Criteria for temporary delay for vaccination

  Administration of any other vaccine 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to ***and after each*** vaccination*.

**** In case emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is organised by public health authorities outside the routine immunisation programme, the time period described above can be reduced if, necessary for that vaccine, provided it is licensed and used according to its Product Information.***

- Section 7.3.1: Emergency unblinding

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

- Table 13: Humoral Immunity (Antibody determination)

  Footnote:

  ******GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart Belgium or Wavre, Belgium~~; Marburg, Germany~~. CLS may delegate testing to GSK Research laboratories in Siena, Italy or to an external laboratory.***

  + The NHBA indicator strain, M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

- Table 14: Immunological read-outs

Blood sampling timepoint		Subset/Sub-cohort Name	No. of subjects/Group	Component	~~Components priority rank~~
Type of contact and timepoint	Sampling timepoint				
Visit 1 (Day 1)	Pre-Vacc	Groups MenB+MenACWY and MenB	315	hSBA-M14459 hSBA-96217 hSBA-NZ98/254 hSBA-M07-0241084*	~~1.1 M14459~~ ~~1.2 96217~~ ~~1.3 NZ98/254~~ ~~1.4 M07-0241084*~~
		Groups MenB+MenACWY and MenACWY	315	hSBA-MenA hSBA-MenC hSBA-MenW hSBA-MenY	~~2.1 MenY~~ ~~2.2 MenW~~ ~~2.3 MenA~~ ~~2.4 MenC~~
Visit 2 (Day 31)	Post Vacc1	Groups MenB+MenACWY and MenB	315	hSBA-M14459 hSBA-96217 hSBA-NZ98/254 hSBA-M07-0241084*	~~1.1 M14459~~ ~~1.2 96217~~ ~~1.3 NZ98/254~~ ~~1.4 M07-0241084*~~
		Groups MenB+MenACWY and MenACWY	315	hSBA-MenA hSBA-MenC hSBA-MenW hSBA-MenY	~~2.1 MenY~~ ~~2.2 MenW~~ ~~2.3 MenA~~ ~~2.4 MenC~~
		Groups MenB+MenACWY and MenACWY	315	ELISA IgG anti meningococcal serogroups A, C, W, Y	~~3 MenA~~ ~~3 MenC~~ ~~3 MenW~~ ~~3 MenY~~
Visit 4 (Day 91)	Post Vacc2	Groups MenB+MenACWY and MenB	315	hSBA-M14459 hSBA-96217 hSBA-NZ98/254 hSBA-M07-0241084*	~~1.1 M14459~~ ~~1.2 96217~~ ~~1.3 NZ98/254~~ ~~1.4 M07-0241084*~~

Footnote: ****The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.***

- Table 15: Reporting periods for collecting safety information

  Footnote: ****Solicited AEs to be collected for 7 days following each vaccination, with ongoing solicited AEs collected until resolution or day 30, whichever occurs first.***

- ***Section 8.4.7: Medical device deficiencies***

  Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is:
  An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

4. ***recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,***
5. ***intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or***
6. ***intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).***

   The study intervention is a combination product constituted of a device and biologic product (e.g. pre-filled syringes). Refer to the Glossary of terms for the definition of combination product and medical device deficiency.

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

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

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 12.7 for definitions and details on recording and reporting of these events.

The sponsor will be the contact for the receipt of device deficiency reports.

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 GSK within 24 hours.

8.4.7.2 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 fulfil 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 section 10.6.3. 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.

- Section 10.1.1.1: Primary Immunogenicity Objectives

  ~~For the testing of the~~***The 8 hypotheses associated with the primary objective will be tested simultaneously, to control for the type I error rate. The testing of the hypotheses will be done simultaneously on all the strains and serogroups.*** a stepwise approach will be used. To control for the type I error rate of α=0.05 (2-sided), the testing of the hypotheses will be done in a predefined order. The approach will start with the first hypothesis and, if rejected, will continue with the same α=0.05 to the next hypothesis in order and will stop at the first hypothesis not rejected. ~~The testing will be done in the following order of the strains: A, C, W, Y, M14459, 96217, NZ98/254 and M07-0241084.~~

- Section 10.1.2: Sample size calculation

  ~~To control for the type I error rate of α=0.05 (2-sided), the testing of the hypotheses will be done in a predefined order. The approach will start with the first hypothesis and, if rejected, will continue with the same α=0.05 to the next hypothesis in order and will stop at the first hypothesis not rejected.~~ The testing ***of the hypotheses will be done simultaneously on all the strains and serogroups.*** ~~will be done in the following order of the strains: A, C, W, Y, M14459, 96217, NZ98/254 and M07-0241084.~~

  ~~For the testing of the hypotheses associated with the primary objective a stepwise approach will be used.~~

- Section 10.3.3: Immunogenicity analyses

  Footnote: ****The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.***

- Section 12.1.2: Glossary of terms

Combination product: ***Combination product comprises any combination of***

- ***drug***
- ***device***
- ***biological product***

Each drug, device and biological product included in a combination product is a constituent part.

***Medical device deficiency**:*	***A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.***

- Section 12.2: Appendix 2: Clinical laboratory assays

  ****The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.***

  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, CFU)~~.

- Table 23: GSK Biologicals laboratories

~~GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany~~	~~Emil-von-Behring-Str. 76, 35041 Marburg, Germany~~

- Table 24: Outsourced laboratories (potential)

CCI [redacted]	[redacted]

- Section 12.4.3: Informed consent process

  The informed consent process may be conducted ***approximately 2 weeks*** ~~up to 5 days~~ prior to vaccination on day 1.

- Section 12.5.3: Solicited adverse events

  The term “reactogenicity” refers to solicited signs and symptoms (“solicited adverse events”) occurring in the hours and days following a vaccination, to be collected by the subjects/parent(s)/LAR(s) for 7 consecutive days ***(with ongoing solicited AEs collected until resolution or day 30, whichever occurs first)***, using a pre-defined Subject Diary.

- Section 12.5.3.1: Other Solicited Adverse Events

  ~~Solicited local or systemic adverse event that continues beyond day 7 after vaccination.~~

- Section 12.5.5.1: Arthritis

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

- Section 12.5.8.2: Time period for detecting and recording adverse events, serious adverse events and pregnancies

Any solicited AE that has not resolved within 30 days post vaccination and is reported during clinic visits or safety follow-up calls will be entered into the subject's eCRF as an unsolicited AE. It will also be included in the subject's source documents at the site by the investigator/site staff as a verbally reported event. It will not be included in the Subject eDiary. These AEs will be analysed as unsolicited AEs (i.e. in the Unsolicited Safety Set).

- ***Section 12.7: Appendix 7: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)***

12.7.1 Definition of medical device AE and adverse device effect (ADE)

Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether 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 an AE related to the use of a medical device. This definition includes any AE resulting from:

- ***insufficient or inadequate instructions for use (i.e. user error), or***
- ***any malfunction of a medical device, or***
- ***intentional misuse of the medical device.***

12.7.2 Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
g. ***Led to death***
h. ***Led to serious deterioration in the health of the participant, that either resulted in:*** • ***A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*** • ***A permanent impairment of a body structure or a body function.*** • ***Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.*** • ***Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function***

i. ***Led to fetal distress, fetal death or a congenital abnormality or birth defect***
j. Is a suspected transmission of any infectious agent via a medicinal product
Serious Adverse Device Effect (SADE) definition
• ***A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.*** • ***Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.***
Unanticipated SADE (USADE) definition
• ***An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 3.3).***

12.7.3 Recording and reporting of medical device AE, ADEs, SADEs and USADE

- ***Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.***
- ***E-mail/Facsimile transmission of the paper 'Medical device or combination product with device deficiency/incident report form' is the preferred method to transmit this information to the sponsor.***
- ***In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of 'Medical device or combination product with device deficiency/incident report form' sent by overnight mail or courier service.***
- ***Contacts for reporting can be found in Section 8.4.6.1.***
- ***GSK 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.***

Detailed description of Protocol Amendment 4:

Additional texts are presented in bold italics and deleted texts are presented in strikethrough.

- Title page: Contributing authors – PPD , Clinical Research and Development Lead
  PPD , Clinical Trials Supply Manager
- Protocol amendment 4 Sponsor signatory page – Short title was replaced with Title.
- Protocol amendment 4 Investigator agreement – Short title was replaced with Title.
- Note for the laboratory assay in Table 3 was updated
  Blood sample collection on Visit 1~~, Visit 2~~ and Visit 4 will be performed before vaccine administration.

CCI

- Section 8.3.2.1: Blood sampling for immunogenicity response assessments
  In clinic visits where a blood draw and a vaccination are planned, ensure that all samples collected for immunogenicity assessments are taken prior to vaccination. The following are clinical circumstances that warrant delay of blood samples collection for immunogenicity assessments in this study:
  - ***Receipt of systemic antibiotics within the previous 3 days (72 hours) before blood sample collection at Visit 1, Visit 2 and Visit 4.***

  In the event that a subject meets the criterion for delay of blood samples collection, blood samples collection may proceed once the appropriate window for delay has passed and vaccination may be delayed as appropriate to ensure sample collection prior to vaccination.
- Section 10.1.2: Sample size calculation
  Standard deviations for hSBA Titer
  For the secondary objective, hypothesis 3, testing of ***MenACWY when given concomitantly with rMenB+OMV NZ to MenACWY***~~rMenB+OMV NZ when~~ ~~given~~

~~concomitantly with MenACWY to rMenB+OMV NZ~~ given alone based on ELISA GMCs, test of treatment Group MenB+MenACWY versus treatment Group ***MenACWY***~~MenB~~, the standard deviations from study V102_02 were used.

- Section 12.1.1: List of abbreviations
  CSR – Clinical study report; SMP – Study management plan

- Section 12.2: Appendix 2: Clinical laboratory assays
  MenACWY serum bactericidal assays using human complement (hSBA) – *Menveo*
  This new hSBA ***that has been*** ~~fully~~ ***validated for the 4 MenACWY*** ~~***serogroups***~~~~under development~~ is also based on the measurement of human complement-dependent bactericidal killing of meningococci.

- Section 12.4.2: Financial disclosure
  Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest***s during the*** ~~prior initiation of the center and at the end of the study. Investigators are responsible for providing an update of financial disclosure if their financial interest changes at any point during their participation in a~~ study and for 1 year after completion of the study.

- Section 12.4.7: Data quality assurance
  Quality tolerance limits (QTLs) will be pre-defined in the Study Management Plan (SMP) to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report (CSR).

Detailed description of Protocol Amendment 3:

Additional texts are presented in bold italics and deleted texts are presented in strikethrough.

- Title page: Co-ordinating author – PPD
- Title page: Contributing authors – PPD, Oversight Data Manager; PPD Clinical Trials Supply Manager; PPD, Clinical Laboratory Sciences Study Manager; PPD SERM Safety Scientist; PPD ***Clinical and Epidemiology Project Leader (CEPL) from Protocol Amendment 3***
- Sponsor signatory page: ~~Daniela Toncatto~~ ***Pavitra Keshavan***, Clinical and Epidemiology Project Lead
- Table 3: Schedule of Activities

Medical History-directed Physical examination	O												See Section 8.2.3 and 8.2.4 for more information.
Symptom-directed physical examination				O		O							See Section ~~8.2.3 and~~ 8.2.4 for more information.

COVID-19 infection-related AEs and SAEs should also be recorded on a separate eCRF page.

- Table 5 Intervals between study visits and safety follow-up calls included

Interval	*Length of interval*	*Allowed interval*
Visit 1 → SFU 1	*14 days*	*11 - 17 days*
Visit 3 → SFU 2	*14 days*	*11 - 17 days*
Visit 4 → SFU 3	*14 days*	*11 - 17 days*
Visit 4 → SFU 4	*90 days*	*83 - 111 days*
Visit 4 → SFU 5	*180 days*	*173 - 201 days*
Visit 4 → SFU 6	*270 days*	*263 - 291 days*
Visit 4 → SFU 7	*360 days*	*353 – 381 days*

- Section 5.2 – Primary completion Date (PCD): ***Study termination-call*** ~~Visit 4 (Day 91~~***Day 451***).
- Section 6.3 – Criteria for temporary delay for vaccination
  A positive test for active COVID-19 within the previous 14 days. The testing should be done using a molecular assay (polymerase chain reaction [PCR]) or antigen test approved by the country regulatory authorities.
  Subjects with known COVID-19 positive contacts in the past 14 days.

- Table 9: Treatments administered

Study Treatment Name:	***Bexsero***	***Menveo******		**Placebo**
Vaccine(s)/Product(s) name	rMenB+OMV NZ	MenA lyo	MenCWY liquid	Placebo (NaCl)
Presentation	*Suspension for injection_Suspension for suspension for injection in a syringe* ~~Suspension for injection in a syringe~~	***Powder for solution for injection in a vial*** ~~Powder for solution for injection in a vial~~	***Solution for solution for injection in a vial*** ~~Solution for injection in a vial~~	Solution for injection in a syringe

Study Treatment Name:	***Bexsero***	***Menveo****	**Placebo**
Vaccines formulation	CCI	CCI CCI	Sodium chloride (NaCl) (0.9%); Water for injections ~~q.s. 0.5 mL~~
Volume to be administered**	0.5 mL	0.5 mL	~~0.5~~ ***0.65 mL*****

** Refer to the SPM for the volume after reconstitution, ***if applicable***.

*** CCI

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

- Table 10: Administration and laterality
  ****Laterality is defined due to multiple vaccinations at different visits; non-dominant arm is the preferred arm for injection, when applicable. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.***

- Table 11: Contact information for emergency unblinding

GSK Helpdesk 24/24 hour and 7/7 day availability
The Helpdesk is available by phone, fax and email Phone: +32.2.656.68.04 ***For US only Toll Free: + 1 844 446 3133*** ***Italy Toll Free: 800 879 197*** For Canada, US and Puerto Rico ***Alternate*** Toll-free number: 877.870.0019 Fax: +32.2.401.25.75 email: rix.ugrdehelpdesk@gsk.com

- Section 8.1 – General study aspects
  During special circumstances, exemplified by the COVID-19 pandemic, certain study procedures may be adapted to protect the subject and promote data integrity. Refer to Section 8.7 for further details

- Section 8.2.3 – Medical history
  ~~A general physical examination is to be performed by a qualified health care professional. "Qualified health care professional" refers to a licensed or certified health care professional with documented training and experience, as determined by the Principal Investigator (PI), and who is permitted by institutional policy to perform protocol required procedures, and who is identified on the Study Staff Signature Log. The physical examination will include a check of general appearance, the measurement of vital signs (body temperature [preferably oral] and heart rate), auscultation of heart and lungs, measurement of length and weight. The medical history-directed exam of other body parts and systems to assess eligibility will be performed during Visit 1.~~

- Section 8.2.4 – Physical examination
  ~~A general p~~ ***Physical examination is to be performed by a qualified health care professional. "Qualified health care professional" refers to a licensed or certified health care professional with documented training and experience, as determined by the Principal Investigator (PI), and who is permitted by institutional policy to perform protocol required procedures, and who is identified on the Study Staff Signature Log.*** ~~The physical examination will include a check of general appearance, the measurement of vital signs (body temperature [preferably oral] and heart rate), auscultation of heart and lungs, measurement of length and weight. Perform a~~***The*** physical examination of the subject ***will include***~~, including~~ assessment of body temperature ***(preferably oral)*** and resting vital signs: systolic/diastolic blood pressure, and heart rate ~~and respiratory rate~~ after at least 10 minutes of rest.
  Medical history-directed physical examination to assess eligibility will be performed during Visit 1.

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

Physical examination at each study visit subsequent to the first vaccination visit, will be performed only if the subject/subject's parent(s)/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate ***(symptom-directed physical examination). These data will be written in the source document. Should the physical assessment reveal any abnormal values or events, these must be documented in the eCRF Adverse Events Form.***

- Section 8.3 – Efficacy assessments
  It is also possible that ~~future~~***further*** findings may make it desirable to use the samples acquired in this study for ***further***~~future~~ research, not described in this protocol. Therefore, all subjects/subjects parent (s)/LAR(s) will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for ***further***~~future~~ research. ***Further***~~Future~~ research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.
- Table 15: Reporting periods for collecting safety information
  Footnote: ****Including COVID-19 infection related AEs.***
- ***Section 8.7: Study procedures during special circumstances***

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

- ***If the eDiary device was provided to the subject, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 5).***
- ***Biological samples may be collected at a different location* other than the study site or at subject's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***

**** It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on subjects by investigator and staff at a site other than the designated study site. Refer to local regulatory guidance on conduct of clinical trials during COVID-19.***

Impact on the Per Protocol Set (PPS) for immunogenicity will be determined on a case by case basis.

- Section 11 – References

World Health Organization (WHO). Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance. WHO, 2019 [cited 11-SEP-2019] Available from: https://www.who.int/publications/i/item/10665-331501

World Health Organization (WHO). WHO COVID-19 Case Definition. WHO, 2020 [cited 11-SEP-2019] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1

- Section 12.1.1 – List of abbreviations
  COVID-19 – Coronavirus disease 2019.
- Section 12.5.8 – Detecting and recording adverse events, serious adverse events and pregnancies
  Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject/subject's parent(s)/LAR(s), but if a person other than the subject/subject's parent(s)/LAR(s) enters information into the Subject Diary, this person's identity must be documented in ~~the Subject Diary~~ ***subject's source record.***
- ***Section 12.5.8.4 - Recording of AEs related to COVID-19***
  For COVID-19 infection-related AEs, sites should follow routine AE/SAE processes as outlined in the protocol, using the following terms according to WHO defined case definitions:
  Suspected COVID-19 case
  Probable COVID-19 case
  Confirmed COVID-19 case [WHO, 2020]
- ***Section 12.5.8.4.1 - WHO Case Definition***
  Suspected COVID-19 case

  A. A person who meets the clinical AND epidemiological criteria.

  Clinical criteria:

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

  AND

  Epidemiological criteria:

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

OR

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

Probable COVID-19 case

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

OR

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

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

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

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

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

OR

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

OR

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

Confirmed COVID-19 case

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

Detailed description of Protocol Amendment 2:

- Inclusion criteria has been updated (Section 6.1): Previous vaccination with one dose of quadrivalent meningococcal conjugate vaccine (MenACWY*, Menveo or Menactra*) at least **4** ~~3~~years prior to informed consent and assent as applicable (according to the subject's age).
- Exclusion criteria has been updated (Section 6.2.1): Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to study vaccination. This will mean prednisone ≥20~~5~~ mg/day (for adult subjects) or ≥0.5 mg/kg/day ***or 20 mg/day whichever is the maximum dose*** for ~~(~~paediatric subjects~~)~~, or equivalent. Inhaled and topical steroids are allowed.
- The End of Study definition (Section 12.1.2) has been updated to adapt to the study design: For studies with collection of human biological samples and/or imaging data, the End of Study is defined as follows: Last subject last visit (***last concluding contact on Day 451*** ~~Visit 4~~) or Last testing results released of samples collected at Visit 4*.

  * In this case EoS must be achieved no later than 8 months after LSLV ***(last concluding contact)***.
- Sentence referring to implausible measurements in Section 10.3.4 has been deleted as this has been explained in Section 12.5.8 of the protocol: ~~Implausible measurements (for further definition see SAP) will be left out of the analysis.~~
- Treatments administered table (Section 7.1; Table 8) has been updated to reflect the correct concentration for rp961c antigen in the *Bexsero* formulation. Additional editorial changes have been included in Table 8, that do not impact the vaccine formulation. As the study will be conducted in the US, EU specifications for the vaccines from the footnote has been deleted.

Study Treatment Name:	***Bexsero***	***Menveo****		**Placebo**
Vaccine(s)/Product(s) name	rMenB+OMV NZ	MenA lyo	MenCWY liquid	Placebo (NaCl)
Presentation	***Suspension for injection in a syringe*** ~~Prefilled syringe (liquid)~~	***Powder for solution for injection in a vial*** ~~Lyophilized component in a vial~~	***Solution for injection in a vial*** ~~Liquid component in a vial~~	***Solution for injection in a syringe*** ~~Prefilled syringe (liquid)~~
Vaccines formulation	CCI [redacted]	[redacted]	[redacted]	***Sodium chloride (NaCl) (0.9%); Water for injections q.s. 0.5 mL***

Study Treatment Name:	***Bexsero***	***Menveo****	**Placebo**
	CCI [redacted]	[redacted]	
~~**Vaccines formulation (in the US)****~~	CCI [redacted]	[redacted]	~~NaCl=150mM~~
Route of Administration	***Intramuscular use*** ~~IM injection~~	***Intramuscular use*** ~~IM injection~~	***Intramuscular use*** ~~IM injection~~

*** *Menveo* commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component, to be reconstituted together before administration (0.5 mL**).** CCI [redacted]

**** CCI [redacted]

Detailed description of Protocol Amendment 1:

The major changes made to this amendment were with regard to transferring the protocol to the GSK protocol template (DS-BIO-CLIN-1000 v16.0) and the incorporation of protocol template-specified mandatory text. These changes have not been listed here. The changes with regard to CBER feedback in the main sections of the protocol are described here.

Throughout the protocol, the study group names were changed as follows:

- Vaccine Group A to Group MenB+MenACWY
- Vaccine Group B to Group MenB
- Vaccine Group C to Group MenACWY

The introduction section and rationale for the study were updated to include the following data from V72_56 infant study, as follows:

Data from an infant study showed that both rMenB+OMV NZ and MenACWY were well tolerated and immunogenic when administered concomitantly in healthy infants. However, no data is currently available on the concomitant use of rMenB+OMV NZ and MenACWY ***in adolescents***.

The success criterion for primary and secondary immunogenicity objectives were re-written for clarity as follows (**Synopsis** and **Section 4**):

Primary Immunogenicity objectives:

- To demonstrate the non-inferiority of the antibody response to rMenB+OMV NZ given concomitantly with MenACWY to healthy subjects 16-18 years of age compared to rMenB+OMV NZ administered without MenACWY, as measured by serum bactericidal assay using human complement (hSBA) Geometric Mean Titers (GMTs) against *N. meningitidis* serogroup B test strains M14459 (fHbp), 96217 (NadA), NZ98/254(PorA) and M07-0241084 (NHBA), at one month after the second vaccination with rMenB+OMV NZ.

  Criterion: Non-inferiority will be demonstrated if for each of the four serogroup B test strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs null hypothesis that the difference in the population means (of the logarithmically [base of 10] transformed hSBA titers) of (rMenB+OMV NZ with MenACWY versus rMenB+OMV NZ alone) is >less than or equal to log10(0.5) is rejected.

- To demonstrate the non-inferiority of the antibody response to MenACWY given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone, as measured by hSBA GMTs against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY.

Criterion: Non-inferiority will be demonstrated if for each of the four serogroups A, C, W and Y, the lower limit of the 2-sided 95% CI of the between-group ratio of hSBA GMTs (null hypothesis that the difference in the population means (of the logarithmically [base of 10] transformed hSBA titers) of rMenB+OMV NZ with MenACWY versus MenACWY alone) is >less than or equal to log10 (0.5) is rejected.

Secondary objectives:

- To assess the non-inferiority of the responses to MenACWY when given concomitantly with rMenB+OMV NZ to healthy subjects 16-18 years of age compared to MenACWY administered alone as measured by ELISA Geometric Mean Concentrations (GMCs) against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY.

  Criterion: Non-inferiority will be demonstrated if for each of the four A, C, W and Y strains, the lower limit of the 2-sided 95% CI of the between-group ratio of ELISA GMCs (null hypothesis that the difference in the population means (of the logarithmically [base of 10] transformed hSBA titers) of MenACWY with rMenB+OMV NZ versus MenACWY alone) is >less than or equal to log10 (0.5) is rejected.

Details regarding the blinding process to the lab personnel performing clinical testing are updated. Following the integration of the two legacy blinding processes with regards to lab personnel, a duly assessment confirmed that the laboratory in charge of the clinical testing can be blinded to the treatment as well as to the subject number. Moreover, in order to prevent the laboratory from linking the consecutive visits to a specific subject, a different subject code will be used for each timepoint tested.

- The 4-fold increase in post-vaccination hSBA titer definition when the pre-vaccination titer is below the LOD, has been modified to: For a pre-vaccination titer < LOD, a post-vaccination titer of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater.

Section 7.5.1, Recording of concomitant medication/products and concomitant vaccinations, the following criteria was added:

- 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.

In **Section 8.2.1 Data collected from subjects,** the following change was made:

- Vaccination history as confirmed by vaccination records, if accessible.
- In Section 8.2.3, Medical history, text on qualified healthcare professional was added as follows:

A general physical examination is to be performed by a qualified health care professional. "Qualified health care professional" refers to a licensed or certified health care professional with documented training and experience, as determined by the Principal Investigator, and who is permitted by institutional policy to perform protocol required procedures, and who is identified on the Study Staff Signature Log.

The physical examination will include a check of general appearance, the measurement of vital signs (body temperature [preferably oral] and heart rate), auscultation of heart and lungs, measurement of length and weight. The medical history-directed exam of other body parts and systems to assess eligibility will be performed during Visit 1.

In **Section 8.2.4, Physical examination**, changes were made to clarify that only abnormal findings from physical examination will be documented in the eCRF. The text was modified as follows:

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

In **Section 8.3.3, Laboratory assays,** the humoral immunity table (Table 12) has been updated to capture the hSBA assay cut-off values (LOD and LLOQ) for MenB and MenACWY.

In **Section 12.5.3.1, Other solicited adverse events**, the following changes were made:

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

The following criteria was added for solicited AEs which need to be entered into subject's source documents and also as an AE on AE eCRF:

- Solicited local or systemic adverse event that continues beyond day 7 after vaccination.

In **Section 12.5.5, Adverse events of special interest,** Arthritis was added as an AESI and following related text was added under Section 12.4.5.1:

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

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

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

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

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