Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA (GSK)

Primary study intervention(s) and number(s)	GSK's combined meningococcal groups A, B, C, W and Y vaccine (GSK4023393A)
Other study intervention(s)	• GSK's combined Meningococcal Groups A, B, C, W and Y vaccine (GSK3536819A) • GSK's meningococcal group B vaccine (*Bexsero*) • Meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (*Nimenrix*)
Study identifier	217043
Abbreviated title	MENACWY=MEN7B-003
EudraCT number	2021-001367-24
Approval date	28 Feb 2024
Title	A Phase II, randomised, partially blinded study to assess the safety, tolerability and immunogenicity of meningococcal combined ABCWY vaccine when administered to healthy infants
Brief title	A study on the safety, tolerability and immune response of meningococcal combined ABCWY vaccine in healthy infants
Sponsor	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Pavitra Keshavan Senior Director, Clinical Project Lead MenABCWY 2nd Gen

Medical monitor name and contact information can be found in the local study contact information document.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.2

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Protocol Amendment 4 Investigator Agreement

- ***To assume responsibility for the proper conduct of the study at this site.***
- ***That I am aware of and will comply with GCP and all applicable regulatory requirements.***
- ***That I will comply with the terms of the clinical study site agreement.***
- ***To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.***
- ***To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.***

Study identifier	217043
Abbreviated title	MENACWY=MEN7B-003
217043udraCT number	2021-001367-24
Approval date	28 Feb 2024
Title	A Phase II, randomised, partially blinded study to assess the safety, tolerability and immunogenicity of meningococcal combined ABCWY vaccine when administered to healthy infants
Investigator name	
Signature	
Date	
Leiter der klinischen Prüfung name, function and title	
Signature	
Date of signature	

Protocol Amendment 4 Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 4	28 Feb 2024
Amendment 3	31 October 2022
Amendment 2	18 February 2022
Amendment 1	01 September 2021
Original Protocol	04 June 2021

Amendment 4 (28 Feb 2024**)**

Overall rationale for the current Amendment:

This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with the latest protocol template.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	**Description of change**	**Brief rationale**
Definitions of terms	Updated information as per the latest protocol template.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 1.1. Synopsis	Added the term “comparator” for *Bexsero* and *Nimenrix v*accine.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 2.1 Study Rationale	Updated information about study restart, total number of participants enrolled, and added the term “comparator” for *Bexsero* and *Nimenrix* vaccine.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 4.1. Overall Design	Added the term “investigational” and “comparator” for vaccines.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 4.1. Overall Design	Rephrased the statement of “Control”.	For better understanding.

Section # and title	Description of change	Brief rationale
Section 4.4 End of Study Definition	Updated information as per the latest protocol template and if testing occurs prior to completion of LSLV.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 5 Study Population	Updated information as per the latest protocol template.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 6.1. Study interventions administered (Table 5 and Table 6)	Added additional information as per the latest template.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 6.1.1. Non-study vaccines	The term “non-study vaccine” was changed to “co-administered vaccines”.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 8.1.3. Immunological read-outs	Added additional information	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 8.2.1.1. Collection of demographic data	Added additional information as per the latest template.	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 8.3.3. Regulatory reporting requirements for SAEs and other events	Added additional information	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 9.4. Interim analyses	Added additional information	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 9.5. Sample size determination	Updated information in Table 17 regarding study groups	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 10.1.4. Data protection	Added additional information	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.

Section # and title	Description of change	Brief rationale
Section 10.1.6. Dissemination of clinical study data	Added additional information	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.
Section 10.1.7. Data quality assurance	Added additional information	This protocol has been amended to align with EU-CTR requirements as part of the CTRIS submission and to ensure cross alignment with update as per the latest protocol template.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE:	Adverse Device Effect
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AO:	Agar-overlay
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CRDL:	Clinical Research and Development Lead
CSR:	Clinical Study Report
CTRIS:	***Center for Translation Research and Implementation Science***
eCRF:	Electronic Case Report Form
eDiary:	Electronic Diary
EoS:	End of Study
Eu-CTR:	***European Clinical Trial Register***
GCP:	Good Clinical Practice
GMT:	Geometric Mean Titre
GSK:	GlaxoSmithKline Biologicals SA
HCP:	Healthcare Professionals
IB:	Investigator's Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IMD:	Invasive Meningococcal Disease
IMP:	***Investigational medicinal product***
IRB:	Institutional Review Board
iSRC:	Internal Safety Review Committee
LAR:	Legally Acceptable Representative
LML	Local Medical Lead
LSLV:	Last Subject Last Visit
MedDra:	Medical Dictionary for Regulatory Activities
MHRA:	Medicines and Healthcare products Regulatory Agency
MoA:	Months of Age
OMV:	Outer Membrane Vesicles
pIMD:	Potential Immune-Mediated Disease
PT:	Preferred Term
QTL:	Quality Tolerance Limit
SADE	Serious Adverse Device Effect
SAE:	Serious Adverse Event
SBIR:	Source data Base for Internet Randomisation
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
SMQ:	Standard MedDRA Query

Abbreviation	Definition
SoA:	Schedule of Activities
SPM:	Study Procedures Manual
SRT:	Safety Review Team
SUSAR:	Suspected Unexpected Serious Adverse Reaction
USADE	Unanticipated Serious Adverse Device Effect
VCSP:	Vaccines Clinical Safety and Pharmacovigilance

Term	Definition
Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, 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.
AxMP	***Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.*** ***Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product.*** ***Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.*** ***Unauthoried AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004.*** ***Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.***
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned. In an observer-blind study, the participant, the site, and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g., double-blinded consistency lots which are open with respect to the control group.

Term	Definition
Caregiver	***A "caregiver" is someone who:*** • ***lives in the close surroundings of a participant and has a continuous caring role or*** • ***has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).*** ***In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.***
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (e.g., 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.
Co-administered product	***A product given to clinical trial participants as required in the protocol as part of their standard care for a condition that is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.***
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.
Comparator	***Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).***
Decentralized trial platform	***A digital engagement technology allowing for the remote delivery and access to trials for participants, sites, and sponsors.***
eDiary	***Electronically recorded patient data and automated data entries on, for example, a handheld mobile device, tablet, or computer.***
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolment	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
HHS	***Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.***
Intercurrent event	***Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.***
Immunological correlate of protection	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.

Term	Definition
Intervention number	A number identifying the intervention assigned to a participant, according to intervention allocation.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
LAR	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
LSLV	***The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).***
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date	This is the date that the final participant in the study was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In other words, Primary Completion Achieved is the date of the last contact with the participant when data has been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. In the case of clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. This date may occur prior to the study end or be the same date as the study end milestone.
Protocol amendment	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	A visit conducted in the place other than the study site.
Self-contained study	Study with objectives not linked to the data of another study.
Solicited event	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the

Term	Definition
	reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Source documents	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Standard of care	***Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.***
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Subcohort	A group of participants for whom specific study procedures are planned as compared with other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule) at the time of enrollment.
SUSAR	***In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.***
Telemedicine	***The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.***
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.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

1. PROTOCOL SUMMARY

1.1. Synopsis *(Amended, 28 Feb 2024)*

Rationale: *Neisseria meningitidis* infections causing invasive meningococcal disease (IMD) are an important public health concern worldwide due to the substantial morbidity and mortality they cause, as well as the transmissibility of these infections. Ninety percent of meningococcal meningitis and septicaemia are caused by only 5 *N. meningitidis* serogroups: A, B, C, W and Y. Infants, young adults, and adults >65 years of age have the highest rates of meningococcal disease in the United States (US) and Europe [CDC, 202***2***; ECDC, 202***2***].

Based upon extensive clinical experience with *Menveo* [Keshavan, 2018] and *Bexsero* [Snape, 2013; Bai, 2011; Watson, 2016; Toneatto, 2017] vaccines, GlaxoSmithKline Biologicals SA (GSK) is currently developing combination vaccines intended to protect against IMD caused by all 5 meningococcal serogroups. An investigational pentavalent MenABCWY vaccine has been tested in Phase I and Phase II clinical studies in participants aged 10 years and older. The final formulation selected is currently tested in Phase III in adolescents and young adults. This combination vaccine contains exactly the same MenACWY-CRM glycoconjugates, in a fully lyophilised formulation, in the same amounts as the licensed *Menveo* vaccine and the same liquid formulation as the licensed *Bexsero* vaccine.

In addition, GSK is developing the investigational MenACWY-7B vaccine, composed of the same MenACWY-CRM glycoconjugates, in a fully lyophilised formulation, in the same amounts as the licensed *Menveo* vaccine and 7 serogroup B (Men7B) antigens which include the 4 MenB antigens present in *Bexsero* (NadA, NHBA-953, 936-fHbp, Outer Membrane Vesicles [OMV]) and 3 additional factor H binding protein (fHbp) CCI [redacted]. A First-Time in Human Phase I/II study is currently ongoing in healthy adults and adolescents and is designed to assess safety, tolerability, effectiveness and immunogenicity of 2 formulations of the investigational MenACWY-7B vaccine, CCI [redacted]

The present study is designed to evaluate the safety, tolerability and immunogenicity in healthy infants 2 months of age (MoA) at enrolment of 2 MenACWY-7B vaccine formulations CCI [redacted] and of the MenABCWY vaccine. ***The comparators*** *Bexsero* (rMenB+OMV NZ, hereafter referred to as MenB) and *Nimenrix* (hereafter referred to as MenACWY-TT) will be administered as control vaccines.

The aim of this study is to provide safety and immunogenicity data in infant population to support the selection of the formulation of the MenACWY-7B vaccine to be tested in Phase III.

This study will also provide first-time safety and immunogenicity data on the MenABCWY vaccine in infant population. Results from Phase II clinical studies in adolescents and young adults showed that MenABCWY vaccine is safe and well tolerated. In this population the reactogenicity of MenABCWY was seen to be comparable to that of *Bexsero,* given either alone or co-administered with *Menveo*, with the OMV component believed to be the main driver of the reactogenicity profile [Block, 2015; Beran, 2021]. *Bexsero* and *Menveo* vaccines also showed to be well tolerated when either co-administered or administered alone in a Phase IIIb study in infants, with no safety issues [Macias Parra, 2018]. Based on the above information, MenABCWY vaccine is expected to have a comparable safety profile in infants as well.

Objectives and endpoints: Refer to Table 3 for the study objectives and endpoints.

1.2. Schema

Refer to Figure 1 in Section 4.1, Overall design.

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities

Age	2 Months	4 Months	5 Months	8 Months	12 Months	13 Months	15 Months	18 Months	Notes
Type of contact	Visit 1	Visit 2	Visit 3	PC 1	Visit 4	Visit 5	PC 2	PC 3	
Timepoints	Day 1	Day 61	Day 91	Day 181	Day 301	Day 331	Day 391	Day 481	
Informed consent	●								Confirm consent form signed prior to any procedures.
Check inclusion/exclusion criteria	●	○			○				Prior to administering each study intervention, the investigator must check eligibility criteria for subsequent vaccinations and criteria for delay of study intervention administration.
Collect demographic data	●								
Medical and vaccination history	●								Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log.
History directed physical examination /Physical examination	○								
Symptom-directed physical examination		○	○		○	○			
Study group and intervention number allocation (randomisation)	●								
Study intervention(s)									
Check contraindications, warnings and precautions to study vaccination	○	○			○				
Check criteria for temporary delay for enrolment and/or study vaccination and/or blood sampling	○	○	○		○	○			
Intervention number allocation for subsequent doses		○			○				
Body temperature before study vaccines administration	●	●			●				Fever is defined as temperature >38.0°C/100.4°F. The preferred location for measuring temperature will be axillary.

Age	2 Months	4 Months	5 Months	8 Months	12 Months	13 Months	15 Months	18 Months	Notes
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**PC 1**	**Visit 4**	**Visit 5**	**PC 2**	**PC 3**	
Timepoints	**Day 1**	**Day 61**	**Day 91**	**Day 181**	**Day 301**	**Day 331**	**Day 391**	**Day 481**	
Study vaccines administration	●	●			●				Note: The following vaccines will be concomitantly administered as routine practice: *Infanrix-Hexa* and *Prevenar 13* at 2, 4, 12 MoA and *Rotarix* at 2 and 4 MoA.
Post Injection Assessment (30 minutes)	●	●			●				See Section 10.3.7.1 for more information
Recording of administered study intervention number	●	●			●				
Distribution of eDiary device/ Install eDiary app on personal device	○	○			○				For eDiary device, at Visit 2, the correct functioning of the device provided at Visit 1 will be checked. For eDiary app installed on personal device, at Visit 2 and Visit 4, the presence of the app will be checked.
Laboratory Assessment									
Blood sampling for antibody determination			●		●	●			Blood volume of around 5* mL of whole blood (ideally minimum 5 mL) will be collected from all the participants. Blood samples will be collected before vaccine administration.
Safety assessments									
Review of eDiary data		●	●			●			
Recording of solicited events (Days 1–7 post-vaccination)	X	x			x				See Section 10.3.7 for more information.
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●	●	●		●	●			
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	●	
Record any intercurrent medical conditions**	●	●	●	●	●	●	●	●	See section 7.1.1
Recording of MAEs, SAEs, AESIs and AEs leading to withdrawal**	●	●	●	●	●	●	●	●	

Age	2 Months	4 Months	5 Months	8 Months	12 Months	13 Months	15 Months	18 Months	Notes
Type of contact	Visit 1	Visit 2	Visit 3	PC 1	Visit 4	Visit 5	PC 2	PC 3	
Timepoints	Day 1	Day 61	Day 91	Day 181	Day 301	Day 331	Day 391	Day 481	
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a parent(s)/LAR(s) signs the consent form to the end of the study.
Return of eDiary device (if applicable)			○			○			The eDiary device will be collected back by the site.
Uninstall eDiary app from personal device (if applicable)						○			
Study Conclusion								●	Participants who terminate the study early are recommended to complete certain study-related procedures. See Section 4.4 for more information.

Note: The double-line border following Day 91 indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Day 91.

● is used to indicate a study procedure that requires documentation in the individual electronic Case Report Form (eCRF).

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

× is used to indicate a study procedure that will be documented in eDiary.

AE, adverse event; AESI, adverse events of special interest; LAR, legally acceptable representative; MAE, medically attended adverse events; MoA, months of age; PC, phone contact; SAE, serious adverse event.

Note: The study timepoints are the same for all groups, irrespective of the staggered enrolment. The participants enrolled in the Part ***I*** are part of the total sample size.

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

**Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs, and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods. In addition, separate COVID-19 specific eCRF form(s) should be completed.

Table 2 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Visit 1→ Visit 2	60 days	55 to 74 days (-5 to +14 days)
Visit 2→ Visit 3	30 days	25 to 44 days (-5 to +14 days)
Visit 2→ Visit 4	240 days	233 to 254 days (-7 to +14 days)
Visit 2→ Phone Contact 1	120 days	115 to 134 days (-5 to +14 days)
Visit 4→ Visit 5	30 days	25 to 44 days (-5 to +14 days)
Visit 4→ Phone Contact 2	90 days	85 to 104 days (-5 to +14 days)
Visit 4→ Phone contact 3	180 days	173 to 194 days (-7 to +14 days)

2. INTRODUCTION

2.1. Study rationale *(Amended, 28 Feb 2024)*

Neisseria meningitidis (N. meningitidis) infections causing invasive meningococcal disease (IMD) are an important public health concern worldwide due to the substantial morbidity and mortality they cause, as well as the transmissibility of these infections. Ninety percent of meningococcal meningitis and septicaemia are caused by only 5 *N.meningitidis* serogroups: A, B, C, W and Y. Infants, young adults, and adults >65 years of age have the highest rates of meningococcal disease in the US and Europe [CDC, 2022; ECDC, 2022].

GlaxoSmithKline Biologicals SA (GSK) has 2 established meningococcal vaccines, the quadrivalent meningococcal ACWY conjugate vaccine (*Menveo*) and the multi-component recombinant meningococcal B vaccine (*Bexsero*).

The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections, allow greater flexibility in dose administration schedules and increase the coverage for meningococcal disease caused by these serogroups worldwide.

Based upon extensive clinical experience with *Menveo* [Keshavan, 2018] and *Bexsero* [Snape, 2013; Bai, 2011; Watson, 2016; Toneatto, 2017] vaccines, GSK is currently developing combination vaccines intended to protect against IMD caused by all 5 meningococcal serogroups. An investigational pentavalent MenABCWY vaccine has been tested in Phase I and Phase II clinical studies in participants aged 10 years and older. The final formulation selected is currently tested in Phase III in adolescents and young adults. This combination vaccine contains exactly the same MenACWY-CRM glycoconjugates, in a fully lyophilised formulation, in the same amounts as the licensed *Menveo* vaccine and the same liquid formulation as the licensed *Bexsero* vaccine.

In addition, GSK is developing the investigational MenACWY-7B vaccine, composed of the same MenACWY-CRM glycoconjugates, in a fully lyophilised formulation, in the same amounts as the licensed *Menveo* vaccine and 7 serogroup B (Men7B) antigens which includes the 4 MenB antigens present in *Bexsero* (NadA, NHBA-953, 936-fHbp, Outer Membrane Vesicles [OMV]) and 3 additional factor H binding protein (fHbp) CCI [redacted].

A First-Time in Human Phase I/II, randomised, controlled study conducted in healthy adults and adolescents, has started in June 2021 and is currently ongoing. The study is designed to assess the safety, effectiveness and immune response of 2 formulations of the investigational MenACWY-7B vaccine, CCI [redacted]. Phase I of the study is completed, enrolling 32 individuals aged 18 to 45 years in ***2*** sequential steps exposing participants to the lower and higher dose of the investigational vaccine. Unblinded safety data from Phase I was reviewed by an internal Safety Review Committee (iSRC) independent from the study team, and no safety concerns were identified. The iSRC recommendation was to continue the study with Phase II as planned, with ***1024*** participants aged 10 to 50 years enrolled. At the time of finalization of this amendment, based on the safety data gathered from ***1024*** individuals aged 10 to 50 years in Phase II, no safety concerns were identified by the study Safety Review Team (SRT).

The present study is designed to evaluate the safety, tolerability and immunogenicity in healthy infants 2 months of age (MoA) at enrolment, of 2 MenACWY-7B vaccine formulations CCI [redacted] and of the MenABCWY vaccine. ***The comparators*** *Bexsero* and *Nimenrix* will be administered as control vaccines.

The aim of this study is to provide safety and immunogenicity data in infant population to support the selection of the formulation of the MenACWY-7B vaccine to be tested in Phase III.

The study vaccination and recruitment were temporary put on hold as a precautionary measure due to fatal events for which the causality has been investigated. Other study procedures (safety follow-up) continued as planned. The case reports demonstrated there is no causality between the fatal events and the investigational products (MenACWY-7B and MenABCWY). After the investigation ***indicated*** a favourable benefit/risk assessment for the study participants, the study ***was restarted*** with updated holding rules for Part II of the study (see Section 8.2.2).

This study will also provide first-time safety and immunogenicity data on the MenABCWY vaccine in infant population. Results from Phase II clinical studies in adolescents and young adults showed that MenABCWY vaccine is safe and well tolerated. In this population, the reactogenicity of MenABCWY was seen to be comparable to that of *Bexsero,* given either alone or co-administered with *Menveo*, with the OMV component believed to be the main driver of the reactogenicity profile [Block, 2015; Beran, 2021]. *Bexsero* and *Menveo* vaccines also showed to be well tolerated when either co-administered or administered alone in a Phase IIIb study in infants, with no safety issues [Macias Parra, 2018]. Based on the information above, MenABCWY vaccine is expected to have a comparable safety profile in infants as well.

2.2. Background

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

IMD occurs when the normally asymptomatically carried encapsulated gram-negative bacterium *N. meningitidis* enters the bloodstream, multiplies and causes sepsis. Once the blood-brain barrier is compromised, development of acute bacterial meningitis represents a neurological emergency and necessitates immediate diagnosis and treatment [Heckenberg, 2014].

Ninety percent of meningococcal meningitis and septicaemia are caused by only 5 *N. meningitidis* serogroups: A, B, C, W and Y. The distribution of serogroups varies geographically and over time. While the disease burden of IMD in higher-income regions, such as Europe and Australia, is largely attributable to serogroup B, in the 'meningitis belt' of sub-Saharan Africa, IMD is predominantly caused by serogroups A and W. In the US, serogroups B, C and Y account for most IMD.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all 5 of the most common serogroups responsible for invasive disease. With evidence of meningococcal epidemiology changing over time and across geographies [Cohn, 2015; Halperin, 2012; Harrison, 2009], a vaccine with the broadest possible coverage is an important step toward a definitive and global solution for meningococcal disease prevention. Refer to Section 2.1 for details on GSK' investigational MenACWY-7B vaccine in development.

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

The meningococcal group B vaccine (*Bexsero*) contains 3 recombinant proteins [factor H binding protein (fHbp), Neisserial adhesin A (NadA), and Neisseria Heparin Binding Antigen (NHBA)], combined with OMV components from the New Zealand outbreak strain NZ98/254. *Bexsero* is immunogenic against the majority of circulating meningococcal serogroup B strains and has acceptable reactogenicity and safety profiles when administered to individuals across age groups. The vaccine is currently approved in

more than 40 countries worldwide. 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.

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical and clinical studies of MenACWY-7B and MenABCWY vaccines.

2.3. Benefit/Risk assessment *(Amended, 28 Feb 2024)*

Detailed information about the known and expected benefits and risks and expected adverse events of MenACWY-7B and MenABCWY vaccines can be found in their respective IBs.

Detailed information about the known and expected benefits and risks and expected adverse events of *Bexsero* (MenB) ***[Bexsero SmPC, 2017]***, *Nimenrix* (MenACWY-TT) ***[Nimenrix SmPC, 2017]***, *Infanrix-Hexa* ***[Infanrix hexa SmPC, 2010]***, *Prevenar 13* ***[Prevenar 13 SmPC, 2014]*** and *Rotarix* ***[Rotarix SmPC, 2016]*** vaccines can be found in the Prescribing Information or Summary of Product Characteristics (SmPC).

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. In order to be able to treat infants with an immediate systemic allergic reaction to vaccination, all infants across all groups will need to remain under close observation for at least 30 minutes after study intervention for Visit 1, Visit 2 and Visit 4 (see Section 6.1).

In terms of study procedures, blood sampling is associated with a risk of local reactions and infection after or during venepuncture. For this reason, blood samples in this study will be obtained by a trained professional and medical assistance will be available. The potential risk of experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the Informed Consent Form (ICF). The amount of blood to be taken for sampling is within the allowed range for this age.

Benefit considerations include:

- Potential benefit of receiving MenABCWY/MenB+MenACWY-TT vaccines in the first year of life.
- Contributing to the process of developing new vaccines against *N. meningitidis*.
- Medical evaluations/assessments associated with this study (e.g., physical examinations).

Overall Benefit: Risk conclusion

Considering the measures taken to minimise risk to participants participating in this study and since MenACWY-7B and MenABCWY vaccines are based on 2 of GSK's meningococcal vaccines (*Menveo* and *Bexsero*, with well-established safety profiles), the potential risks associated with these investigational vaccines are justified by the anticipated benefits that may be afforded by participants receiving them.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Study objectives, endpoints and estimands

Objectives	Endpoint(s) and estimand(s)
Primary	
• To evaluate the safety and reactogenicity of the MenACWY-7B vaccine CCI [redacted] the MenABCWY vaccine, the MenB vaccine and the MenACWY-TT vaccine.	• The number and percentages of participants with solicited administration site events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301. • The number and percentages of participants with solicited systemic events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301. • The number and percentages of participants with any unsolicited adverse events (AEs) (including all medically attended adverse events [MAEs], serious adverse events [SAEs], AEs leading to withdrawal, and adverse events of special interest [AESIs]) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301. • The number and percentages of participants with MAEs, SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 481).
• To assess the immune response to the MenACWY-7B vaccine CCI [redacted] to the MenABCWY vaccine and to the MenB vaccine against all serogroup B indicator strains*.	• The percentages of participants with human serum bactericidal assay (hSBA) titres ≥lower limit of quantitation (LLOQ) for each serogroup B indicator strain at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331) • hSBA geometric mean titres (GMTs) for each serogroup B indicator strain at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331). • hSBA geometric mean ratios (GMRs) for each serogroup B indicator strain at 1 month after the third vaccination (Day 331) compared to pre-third vaccination (Day 301).
• To assess the immune response to the MenACWY-7B vaccine CCI [redacted] to the MenABCWY vaccine and to the MenACWY-TT vaccine against serogroups A, C, W and Y.	• The percentages of participants with hSBA titres ≥LLOQ for each A, C, W and Y serogroup at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331). • hSBA GMTs for each A, C, W and Y serogroup at: – 1 month after the second vaccination (Day 91) – pre-third vaccination (Day 301) – 1 month after the third vaccination (Day 331). • hSBA GMRs for each A, C, W and Y serogroup at 1 month after the third vaccination (Day 331) compared to pre-third vaccination (Day 301).

*Immune response will be assessed using hSBAs against *N. meningitidis* serogroup B indicator strains CCI [redacted].

Details related to attributes of estimand covering intercurrent events, population and treatment definition are provided in the Section 9.

4. STUDY DESIGN

4.1. Overall design *(Amended, 28 Feb 2024)*

This is a Phase II, randomised, partially blinded, multi-country, self-contained study comprising of 2 parts designed to ensure the safety of participants (see Figure 1).

Part I of the study will include 4 study groups (2 groups in Step 1 and 2 groups in Step 2, randomised 3:1 in both steps) enrolled with a staggered approach (20 participants in Step 1 followed by 20 participants in Step 2) for a total of 40 participants (Figure 1).

The administration of the second vaccination in Step 1 and the enrolment in Step 2 will start only after a positive outcome following the Independent Data Monitoring Committee (IDMC) review of the safety data from participants receiving first dose in Step 1 (for details regarding safety assessment, please refer to Section 8).

Step 1:

- **ACWY-7B[redacted]**: Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT:** Participants will receive 3 doses of both ***comparators*** MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA, as control for the ACWY-7B[redacted] group.

Step 2:

- **ACWY-7B[redacted]:** Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT:** Participants will receive 3 doses of both ***comparators*** MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA, as control for the ACWY-7B[redacted] group.

Part II will start only after a positive outcome following IDMC review of the safety data from all participants receiving the first dose of both lower-dosage (MenACWY-7B[redacted]) and higher-dosage (MenACWY-7B[redacted]) vaccine formulations in Part I of the study (see Section 8 for details on IDMC reviews).

In Part II, ***approximately*** 648 eligible participants will be randomly assigned to 4 study groups in a 1:1:1:1 ratio:

- **ABCWY:** Participants will receive 3 doses of the ***investigational*** MenABCWY vaccine at 2, 4 and 12 MoA.
- **ACWY-7B[redacted]:** Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **ACWY-7B[redacted]:** Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.

- **MenB+MenACWY-TT:** Participants will receive 3 doses of both ***comparators*** MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA.

Note: The following non-study vaccines will be concomitantly administered as routine practice at study visits: *Infanrix-Hexa* and *Prevenar 13* at 2, 4, 12 MoA and *Rotarix* at 2 and 4 MoA. For more detailed information on study groups and treatments administered, refer to Table 4 and Table 5.

Duration of the study: The intended duration of the study, per participant, is approximately 16 months.

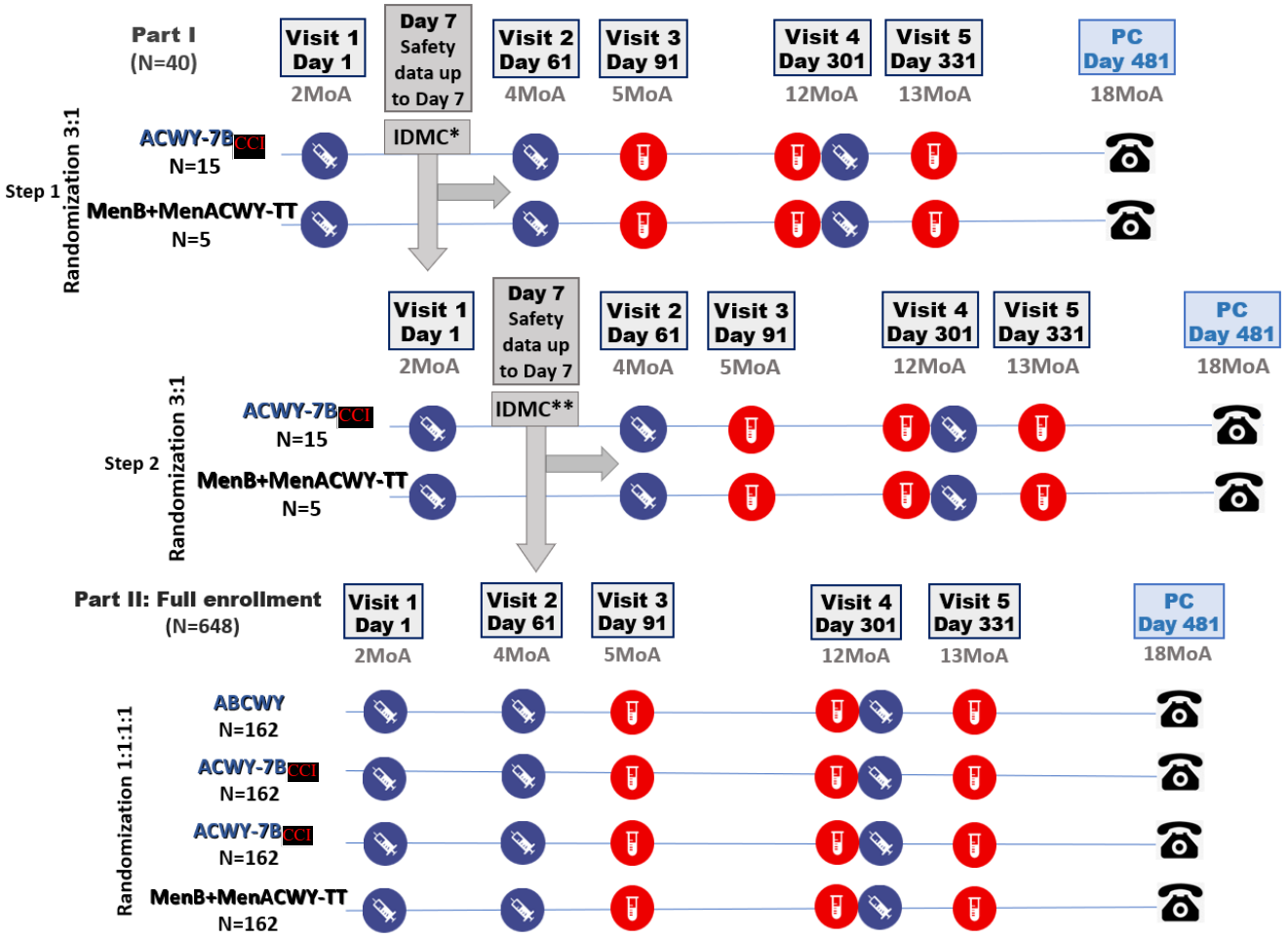
Control: ***Men B and MenACWY-TT vaccines will be active comparators administered at 2, 4 and 12 MoA***.

Blinding: partially blinding (refer to Section 6.3.5 for details on blinding and unblinding procedures).

Sampling schedule: Blood samples for immune response assessment will be collected from all participants at Visit 3 (Day 91), Visit 4 (Day 301) and Visit 5 (Day 331).

The **primary completion date** for the study is the Day 481 Phone Contact. Refer to Section 9.4.2 for the planned interim analysis.

Figure 1 Study design overview



MoA, months of age; N, number of participants; IDMC, Independent Data Monitoring Committee; PC, phone call.

blood sampling; study intervention administration; phone contact

* In Step 1, the IDMC will evaluate safety data up to Day 7 from all participants from ACWY-7B[redacted] and MenB+MenACWY-TT groups (15 and 5 participants per group, respectively). If favourable outcome, the enrolment in ACWY-7B[redacted] and MenB+MenACWY-TT groups will start (Step 2) and the administration of the second vaccination will take place in groups ACWY-7B[redacted] and MenB+MenACWY-TT.

** In Step 2, the IDMC will evaluate safety data up to Day 7 from all participants from ACWY-7B[redacted] and MenB+MenACWY-TT groups (15 and 5 participants per group, respectively). If favourable outcome, the full enrolment will start (Part 2) and the administration of the second vaccination will take place in ACWY-7B[redacted] and MenB+MenACWY-TT groups.

Note 1: This figure represents the main aspects of the study design. Refer to Table 1, SoA, for details on all visits and contacts.

Note 2: For details regarding study groups, blinding and intervention administered within the study refer to Table 4.

Table 4 Study groups, intervention and blinding

Study groups	Number of participants	Age	Study interventions	Blinding	
				Part 1	Part 2
ABCWY	162	2 Months	MenABCWY	-	Observer-blinded
ACWY-7B[redacted]	177*		MenACWY-7B[redacted]	Open label	Observer-blinded
ACWY-7B[redacted]	177*		MenACWY-7B[redacted]	Open label	Observer-blinded
MenB+MenACWY-TT	172*		rMenB+OMV NZ	Open label	Open label
			MenACWY-TT		

* Groups ACWY-7B[redacted] ACWY-7B[redacted] and MenB+MenACWY-TT include the participants enrolled in both parts of the study.

Note: The following vaccines will be concomitantly administered as routine practice: *Infanrix-Hexa* and *Prevenar 13* at 2, 4, 12 MoA and *Rotarix* at 2 and 4 MoA.

4.2. Scientific rationale for study design

The investigational MenACWY-7B vaccine is composed of 4 CRM_{197} glycoconjugates from meningococcal serogroups A, C, W and Y that are identical to those present in *Menveo*, and the 4 MenB antigens present in *Bexsero* (NadA, NHBA-953, 936-fHbp, OMV) along with 3 additional fHbp CCI [redacted].

As the investigational MenACWY-7B vaccine has never been administered to infants, the study will follow a staggered design with 2 parts, in order to assess the safety of the new vaccine first in a small group of healthy infants (Part I) prior to proceeding with the full enrolment in Part II.

Part I of the study will also follow a staggered enrolment with 2 steps, in order to assess the safety of a lower dose of MenACWY-7B vaccine first, in a small number of healthy infants, followed by the higher dose of MenACWY-7B vaccine, if no safety signal is observed during the IDMC reviews (please refer to Section 8.2.2 for study holding rules and safety monitoring).

This study will also provide first-time safety and immunogenicity data on the MenABCWY vaccine in infant population. Results from Phase II clinical studies in adolescents and young adults showed that MenABCWY vaccine is safe and well tolerated. In this population the reactogenicity of MenABCWY was seen to be comparable to that of *Bexsero,* given either alone or co-administered with *Menveo*, with the OMV component believed to be the main driver of the reactogenicity profile [Block, 2015; Beran, 2021]. *Bexsero* and *Menveo* vaccines also showed to be well tolerated when either co-administered or administered alone in a Phase IIIb study in infants, with no safety issues [Macias Parra, 2018]. Based on the above information, MenABCWY vaccine is expected to have a comparable safety profile in infants as well.

CCI [redacted]

CCI

[redacted]

4.4. End of Study definition *(Amended, 28 Feb 2024)*

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

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

End of Study (EoS): Date of the last testing/reading released of the Human Biological Samples, related to primary endpoints. EoS must be achieved no later than 8 months after Last Subject Last Visit (LSLV). ***If the completion of testing occurs prior the completion of the LSLV the latter date defines the EoS.***

5. STUDY POPULATION *(Amended, 28 Feb 2024)*

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

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Participants' parent(s)/LAR(s) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the eDiaries, return for follow-up visits and is available for telephone calls). ***INC#1***
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the participant prior to performance of any study specific procedure. ***INC#2***
- Healthy participants as established by medical history and clinical examination before entering into the study. ***INC#3***
- A male or female between, and including, 55 and 89 days of age (approximately 2 MoA) at the time of the first study vaccination. ***INC#4***

- Born after a gestation period of ≥37 weeks, with a birth weight ≥2.5 kg. ***INC#5***

5.2. Exclusion criteria

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

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

The following criteria should be checked at the time of study entry. ***Participants are excluded from the study if any of the following criteria apply:***

5.2.1. Medical conditions

- Current or previous, confirmed or suspected disease caused by *N. meningitidis*. ***EXC#1***
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection from birth. ***EXC#2***
- Progressive, unstable or uncontrolled clinical conditions. ***EXC#3***
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws. ***EXC#4***
- Any neuroinflammatory disorders (including but not limited to: demyelinating disorders, encephalitis or myelitis of any origin), congenital and peripartum neurological conditions, encephalopathies, seizures (including all subtypes such as: absence seizures, generalised tonic-clonic seizures, partial complex seizures, partial simple seizures or febrile convulsions). ***EXC#5***
- Congenital or peripartum disorders resulting in a chronic condition (including but not limited to chromosomal abnormalities, cerebral palsy, metabolism or synthesis disorders, cardiac disorders). ***EXC#6***
- Major congenital defects, as assessed by the investigator. ***EXC#7***
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s)/product(s). ***EXC#8***
- Hypersensitivity, including allergy, to any component of vaccines, including diphtheria toxoid (CRM_{197}) and latex medicinal products or medical equipment whose use is foreseen in this study. ***EXC#9***
- Abnormal function or modification of the immune system resulting from: ***EXC#10***
  - Autoimmune disorders (including, but not limited to: blood, endocrine, hepatic, muscular, nervous system or skin autoimmune disorders; lupus erythematosus

and associated conditions; rheumatoid arthritis and associated conditions; scleroderma and associated disorders) or immunodeficiency syndromes (including, but not limited to: acquired immunodeficiency syndromes and primary immunodeficiency syndromes).

- Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days starting from birth until Visit 5. This will mean prednisone equivalent ≥0.5 mg/kg/day with maximum 20 mg/day. Inhaled and topical steroids are allowed.
- Administration of antineoplastic and immunomodulating agents or radiotherapy from birth.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).

- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study. ***EXC#11***

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccines from birth, or planned use during the study period. ***EXC#12***
- Previous vaccination with any meningococcal vaccine. ***EXC#13***
- Administration of immunoglobulins and/or any blood products or plasma derivatives from birth or planned administration during the study period until Visit 5. ***EXC#14***
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting from birth until Visit 5. For corticosteroids, this will mean prednisone equivalent ≥0.5 mg/kg/day with maximum 20 mg/day. Inhaled and topical steroids are allowed. ***EXC#15***

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device). ***EXC#16***

5.2.4. Other exclusions

- Child in care (Please refer to the ***DEFINITIONS OF TERMS*** for the definition of child in care). ***EXC#17***
- Study personnel as an immediate family or household member. ***EXC#18***
- For contraindications to administering routine vaccines foreseen in the study (see Table 6), refer to their approved product label/package insert. ***EXC#19***

5.3. Lifestyle considerations

Not applicable.

5.4. Screening failures

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. A screening failure is an individual who consents to participate in this study but is not entered in the study/ randomised to a study intervention.

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

5.5. Criteria for temporarily delaying enrolment/ randomisation/ study intervention administration/ blood sample

Enrolment/randomisation/study intervention administration/blood sample collection may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of enrolment and/or study intervention administration. Refer to the SoA for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Use of antibiotics within 3 days prior to sampling visits.
- Significant acute illness within the previous 7 days of study intervention administration.
- A positive test for current COVID-19 infection prior to intervention administration. The testing should have been done using a molecular (polymerase chain reaction [PCR]) or antigenic test approved by the country regulatory authorities.
- Participants with known COVID-19 positive contacts and considered at risk of having contracted a COVID-19 infection according to local regulations.
- Administration of any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to and following each vaccination up to Visit 4*.

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

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

its Prescribing Information and according to the local governmental recommendations.

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

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study interventions administered

The study interventions (refer to the ***DEFINITIONS OF TERMS*** for the definition of study intervention) will be provided by the sponsor. All study participants are expected to receive these study interventions as specified by the study schedule. The study vaccines specific to this study are described in Table 5.

Table 5 Study interventions administered (*Amended, 28 Feb 2024*)

Study intervention *name*:	**MenACWY-7B[CCI][1]**		**MenACWY-7B[CCI][1]**		**MenABCWY[2]**		***Bexsero***	***Nimenrix***	
***Study intervention formulation*†**	[CCI]	MenA (10 µg)-CRM_{197}; MenC (5 µg) - CRM_{197}, MenW135 (5 µg)- CRM_{197}; MenY (5 µg)-CRM_{197}	[CCI]	MenA (10 µg)-CRM_{197}; MenC (5 µg)- CRM_{197}; MenW135 (5 µg) - CRM_{197}; MenY (5 µg)-CRM_{197}	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHbp fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL[5]	MenA (10 µg)-CRM_{197}; MenC (5 µg)- CRM_{197}; MenW135 (5 µg)- CRM_{197}; MenY (5 µg)-CRM_{197}	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHbp fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL	MenA (5 µg)-TT; MenC (5 µg)-TT; MenY (5 µg)-TT; MenW-135 (5 µg)-TT	Sodium chloride; Water for ***injection*** q.s. 0.5 mL
Presentation	Suspension for suspension for injection/Syringe	Powder for suspension for injection/Vial	Suspension for suspension for injection/Syringe	Powder for suspension for injection/Vial	Suspension for suspension for injection/Syringe	Powder for suspension for injection/Vial	Suspension for injection/Syringe	Powder for solution for injection/ Vial	Solution for solution for injection/ Syringe

Type	***Combination product***	***Combination product***	***Combination product***	***Combination product***	***Combination product***
Use	***Investigational medicinal product***	***Investigational medicinal product***	***Investigational medicinal product***	***Comparator***	***Comparator***
Authorized AxMP/ Unauthorized AxMP	***Not applicable***	***Not applicable***	***Not applicable***	***Not applicable***	***Not applicable***
Route of administration	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use
Administration site[3]					
Location	Thigh	Thigh	Thigh	Thigh	Thigh
Directionality	Upper	Upper	Upper	Upper	Lower
Laterality	Right	Right	Right	Right	Right
No. of doses *to be administered*	3	3	3	3	3
Volume to be administered *by dose*	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Sourcing	***Provided centrally by the sponsor***				
Packaging *and* labelling	Refer to the Study Procedures Manual for more details				
Manufacturer	GSK	GSK	GSK	GSK	Pfizer

Study intervention *name*:	**MenACWY-7B[CCI][1]**		**MenACWY-7B[CCI][1]**		**MenABCWY[2]**		***Bexsero***	***Nimenrix***	
***Study intervention formulation*†**	CCI	MenA (10 µg)-CRM_{197}; MenC (5 µg) - CRM_{197}, MenW135 (5 µg)- CRM_{197}; MenY (5 µg)-CRM_{197}	CCI	MenA (10 µg)-CRM_{197}; MenC (5 µg)- CRM_{197}; MenW135 (5 µg) - CRM_{197}; MenY (5 µg)-CRM_{197}	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHbp fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL[5]	MenA (10 µg)-CRM_{197}; MenC (5 µg)- CRM_{197}; MenW135 (5 µg)- CRM_{197}; MenY (5 µg)-CRM_{197}	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHbp fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL	MenA (5 µg)-TT; MenC (5 µg)-TT; MenY (5 µg)-TT; MenW-135 (5 µg)-TT	Sodium chloride; Water for ***injection*** q.s. 0.5 mL
Presentation	Suspension for suspension for injection/Syringe	Powder for suspension for injection/Vial	Suspension for suspension for injection/Syringe	Powder for suspension for injection/Vial	Suspension for suspension for injection/Syringe	Powder for suspension for injection/Vial	Suspension for injection/Syringe	Powder for solution for injection/ Vial	Solution for solution for injection/ Syringe

Type	***Combination product***	***Combination product***	***Combination product***	***Combination product***	***Combination product***
Use	***Investigational medicinal product***	***Investigational medicinal product***	***Investigational medicinal product***	***Comparator***	***Comparator***
Authorized AxMP/ Unauthorized AxMP	***Not applicable***	***Not applicable***	***Not applicable***	***Not applicable***	***Not applicable***
Route of administration	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use
Administration site[3]					
Location	Thigh	Thigh	Thigh	Thigh	Thigh
Directionality	Upper	Upper	Upper	Upper	Lower
Laterality	Right	Right	Right	Right	Right
No. of doses *to be administered*	3	3	3	3	3
Volume to be administered *by dose*	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Sourcing	***Provided centrally by the sponsor***				
Packaging *and* labelling	Refer to the Study Procedures Manual for more details				
Manufacturer	GSK	GSK	GSK	GSK	Pfizer

† The composition per dose is presented here.

[1] MenACWY-7B[redacted] and MenACWY-7B[redacted] formulations consisting of MenACWY (powder for suspension) and of Men7B (suspension for suspension), to be reconstituted together before administration by a qualified healthcare professional.

[2] MenABCWY consisting of MenACWY (powder for suspension), to be reconstituted together with MenB (suspension for suspension) before administration (0.5 mL) by a qualified healthcare professional.

[3] Site mentioned is the preferred location for injection. Please note however that the investigational vaccines and the concomitantly administered routine vaccines should not be administered in the same thigh.

6.1.1. Non-study vaccines *(Amended, 28 Feb 2024)*

The investigator is responsible for reporting AEs associated ***with co-administered vaccines*** according to local laws and regulations in addition to the safety reporting procedures foreseen in this study. The sponsor is responsible for the ongoing safety evaluation of the clinical trial participants including events related to ***co-administered vaccines***.

The following ***co-administered vaccines*** will be centrally supplied by the sponsor (see Table 6 for details) and will be administered at study visits: *Infanrix-Hexa* and *Prevenar 13* at 2, 4, 12 MoA and *Rotarix* at 2 and 4 MoA. They will be recorded in the participants' eCRF.

Note: Depending on local requirements, other non-study routine vaccines or additional doses of the above-mentioned vaccines may by administered by the clinical study staff during the study period in order to avoid participants to go to different centres to receive the needed vaccines in accordance with the country national immunization program. Additional routine vaccines may be provided by the sponsor or by the clinical study staff and reimbursed by the sponsor, where applicable. Those vaccines should be administered outside a period of 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to and following each vaccination up to Visit 4.

Table 6 Concomitantly administered routine non-study vaccines *(Amended, 28 Feb 2024)*

Study intervention *name*:	***Rotarix****	***Rotarix PCV-free****	***Prevenar 13***	***Infanrix-Hexa***	
Study intervention formulation†	HRV RIX4414 strain (≥1×$10^{6.0}$ $CCID_{50}$); Sterile water q.s. 1.5 mL	HRV RIX4414 strain (≥1×$10^{6.0}$ $CCID_{50}$); Sterile water q.s. 1.5 mL	PS1 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS3 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS4 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS5 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS6A (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS6B (4.4 µg)-CRM_{197} adsorbed on aluminium phosphate; PS7F (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS9V (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS14 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS18C (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS19A (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS19F (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS23F (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; Aluminium phosphate (0.125 mg Al^{3+}); Water for injections q.s. 0.5 mL	DT (≥30 IU) adsorbed on aluminium hydroxide; TT (≥40 IU) adsorbed on aluminium hydroxide; PT (25 µg) adsorbed on aluminium hydroxide; FHA (25 µg) adsorbed on aluminium hydroxide; PRN (8 µg) adsorbed on aluminium hydroxide; HbsAg (10 µg) adsorbed on aluminium phosphate; IPV1 (Mahoney strain) (40 D-antigen units); IPV2 (MEF-1 strain) (8 D-antigen units); IPV3 (Saukett strain) (32 D-antigen units); Aluminium hydroxide ($Al(OH)_3$)/Aluminium phosphate ($AlPO_4$) (0.7 mg Al^{3+}); Water for injections q.s 0.5 mL	Hib (10 µg)-TT(~ 25 µg) adsorbed on aluminium phosphate; Aluminium phosphate
Presentation	Oral suspension/Tube	Oral suspension/Tube	Suspension for injection	Suspension for suspension for injection/Syringe	Powder for suspension for injection/Vial
Type	***Combination product***	***Combination product***	***Biologic product***	***Combination product***	
Use	***Co-administered product***	***Co-administered product***	***Co-administered product***	***Co-administered product***	
Authorized AxMP/ Unauthorized AxMP	***Authorized AxMP***	***Authorized AxMP***	***Authorized AxMP***	***Authorized AxMP***	
Route of administration	Oral use	Oral use	Intramuscular use	Intramuscular use	

Study intervention *name*:	***Rotarix****	***Rotarix PCV-free****	***Prevenar 13***	***Infanrix-Hexa***
Administration site[1]				
Location			Thigh	Thigh
Directionality			Lower	Upper
Laterality			Left	Left
No. of doses *to be administered*	2	2	3	3
Volume to be administered *by dose*	1.5 mL	1.5 mL	0.5 mL	0.5 mL
Sourcing	***Provided centrally by the sponsor***			
Packaging *and* labelling:	Refer to the SPM for more details			
Manufacturer:	GSK	GSK	Pfizer	GSK

* Only one *Rotarix* vaccine formulation/presentation will be co-administered per ***participant***, depending on the country.

† The composition per dose is presented here.

[1] Site mentioned is the preferred location for injection. Please note however that the investigational vaccines and the concomitantly administered routine vaccines should not be administered in the same thigh.

Study participants must be observed closely for at least 30 minutes after the administration of the study interventions. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

6.2. Preparation, handling, storage, and accountability

The study interventions and concomitantly administered non-study vaccines must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorised study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the Study Procedures Manual (SPM) for more details on storage and handling of the study interventions and concomitantly administered non-study vaccines.

6.3. Measures to minimise bias: randomisation and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the individuals who have consented to participate in the study. Each study centre will be allocated a range of participant identification numbers.

6.3.2. Randomisation to study intervention

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

6.3.3. Intervention allocation to the participant

The randomisation algorithm will use a minimisation procedure accounting for study.

Once a participant identification number is allocated, the randomisation system will determine study group and will provide the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (SBIR). Concomitantly administered non-study vaccines will be allocated via SBIR. As well.

When SBIR is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information about interventions number allocation.

6.3.4. Allocation of participants to assay subsets

Not applicable.

6.3.5. Blinding and unblinding

In Part 1, data will be collected in an open label manner.

In Part 2, data will be collected in an observer-blind manner, only for the MenACWY-7B[redacted], Men ACWY-7B[redacted] and MenABCWY arms. To do so, study interventions will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety, efficacy).

The central laboratory in charge of sample testing will be blinded to the study intervention assignment as well as to the subject number. There will be no link between the study intervention groups and the identity of the participant. In addition, for each sample, a different randomly selected participant code will be used at each timepoint. This participant coding will prevent the testing laboratory personnel from linking the consecutive timepoints to a specific participant.

Emergency unblinding

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

In case of emergency, the investigator can have unrestricted, immediate and direct access to the participant's study intervention information via an automated Internet-based system (SBIR). The investigator may contact a GSK Helpdesk (refer to Table 7) if he/she needs help to access participant's study intervention information (i.e. if the investigator is unable to access SBIR).

A physician other than the investigator (e.g. an emergency room physician) or participant/participant's care giver or family member may also request emergency access to the participant's study intervention information either via the investigator or investigator's back up (preferred option) or via the GSK Helpdesk (back up option). The subject/participant card provides contact information for the investigator, his/her back up and GSK Helpdesk.

Table 7 Contact information for emergency unblinding

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

Refer to the SPM for country-specific numbers.

6.3.5.1. Unblinding prior to regulatory reporting of SAEs

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study interventions, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.9.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a SAE that is fatal or life-threatening. For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study intervention compliance

When the study intervention and non-study routine vaccines are administered at the site, participants will receive them directly from the investigator or designee, under medical supervision. The date of administration of each intervention dose in the clinic will be recorded in the source documents.

6.5. Dose modification

Section is not applicable.

6.6. Continued access to study intervention after the end of the study

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

It is the responsibility of the investigator to determine the medical care of the non-responder as per local/regional practices, such as re-vaccination.

6.7. Treatment of overdose

Not applicable.

6.8. Concomitant therapy

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

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

- All concomitant medication associated with an AEs, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention (Day 1 to Day 481).

- Any concomitant vaccination administered in the period starting from birth and ending at the last study contact (Day 481).
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Refer to Sections 5.2.2 and 9.2.1 for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE/Adverse Event of Special Interest (AESI) including vaccines/products, as defined in Sections 8.3.1 and 10.3.7. These must also be recorded in 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.
- The use of analgesics to prevent (prophylactic use) and/or treat pain during the first 7 days after vaccination.

  Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present. An anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (refer to Table 1 for fever definition).

  Prophylactic administration of antipyretics at the time of and closely after vaccination is advised, as this can reduce post-vaccination febrile reactions. This may be initiated according to the investigator's judgement.

  The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications eCRF.

  The use of systemic antibiotics within 3 days prior to blood sampling visit is a reason to delay of blood sample withdrawal (see Section 5.5, Criteria for temporary Delay of Vaccination).

The Local Medical Lead (LML) should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g. safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- AEs requiring expedited reporting to GSK
- Unsolicited non-serious AEs
- Solicited AEs
- Not willing to be vaccinated
- Other (specify).

7.1.1. Contraindications to subsequent study intervention(s) administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below or criteria listed in sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (Section 10.3.7.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Any occurrence of an event listed in the exclusion criteria which must be always re-assessed by the investigator before administration of the next dose of study vaccine.
- Anaphylaxis following the administration of study interventions.
- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Any condition that in the judgement of the investigator would make intramuscular injection unsafe.
- Occurrence of a new AESI or the exacerbation of an existing AESI that, in the opinion of the investigator, exposes the participant to unacceptable risk from subsequent doses of study intervention. Refer to Section 10.3.5 for the definition of AESIs.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for him/her since the date of withdrawal/last contact.

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

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

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

- AEs requiring expedited reporting to GSK (refer to section 10.3.9.1 for details)
- Unsolicited non-serious AEs
- Solicited AEs
- Withdrawal by participant, not due to an AEs*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.7.2).

7.3. Lost to follow-up

A participant will be considered 'lost to follow-up' if he/she fails to return for scheduled visits and cannot be contacted by the study site.

Please refer to the SPM for a description of actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarised in the SoA (Section 1.3).

All screening evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g. haematologic profiles), and obtained before the participant's parent(s)/LAR(s) signed the ICF, may be used for screening and/or for establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA [Section 1.3]).

The SPM provides the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

Burden of the study, degree of strain and risk threshold:

Participants are required to attend 5 visits, to receive the study interventions and perform 3 blood tests. Parent(s)/LAR(s)/Caregiver(s) are required to attend 5 visits and be available for 3 phone contacts during the duration of the trial to perform safety follow-up. A basic, routine medical assessment, including interview on past and current medical history, will also be performed by the investigator or designated person. Participants are not required to undergo any screening procedure or investigation that is outside what is usually provided during a routine medical appointment where a vaccine is administered. An amount of 5 mL of blood is required at each of the 3 sampling visits, which is in line with international recommendation on blood sampling in infants involved in clinical research. The risk benefit assessment and the safety of the investigational vaccine are described in Section 2.3.

Decentralised study procedures

If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. telemedicine, home visits) for the collection of biological samples and/or safety data/safety assessment(s)/study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Refer to the SoA for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM.

Following procedures can be performed remotely/virtually. Refer to the ***DEFINITIONS OF TERMS*** for the definitions of telemedicine, remote and virtual visits:

- Safety follow-up may be performed by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with the participant and monitoring the participant's progress. In addition, qualified study staff/HCPs may also identify AEs and report them to the investigator for evaluation.
- Biological samples may be collected remotely by qualified study staff/HCPs. Biological samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use.
- Administration of study intervention can be performed remotely/at participant's home by qualified study staff/HCPs if appropriate storage conditions for the study intervention can be ensured. Furthermore, appropriate medical treatment must be readily available during 30 minutes after dosing in case of anaphylaxis, syncope.

Study procedures in 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 participants:

- If the eDiary device was provided to the participant, 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 participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- Study visits may be performed at a different location** other than the study site (e.g. at participant's home). For study visits involving blood draw, biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 2), then the interval may be extended as presented in Table 8.
- If despite best efforts it is not possible to administer the dose of study intervention within the interval predefined in the protocol (see Table 2), the interval may be extended as presented in Table 8.

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

** In case of home visits, the study procedures should be carried out by a qualified person/s as delegated by the principal investigator, provided that the compliance with protocol procedures are ensured. Refer to SoA for the schedule of visits (see Table 1).

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

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

Table 8 Intervals between study visits during special circumstances

Interval	Planned visit interval	Allowed interval range
Visit 1→ Visit 2	60 days	53 to 81 days (-7 to +21 days)
Visit 2→ Visit 3	30 days	23 to 51 days (-7 to +21 days)
Visit 2→ Visit 4	240 days	233 to 261 days (-10 to +28 days)
Visit 2→ Phone Contact 1	120 days	113 to 141 days (-7 to +21 days)
Visit 4→ Visit 5	30 days	23 to 51 days (-7 to +21 days)
Visit 4→ Phone Contact 2	90 days	83 to 111 days (-7 to +21 days)
Visit 4→ Phone Contact 3	180 days	173 to 201 days (-7 to +21 days)

8.1. Immunogenicity assessments

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

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

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples

At each sampling visit, blood volume of around 5 mL of whole blood (ideally minimum 5 mL) will be collected from all the participants, to achieve a minimum volume of approximately 2 mL of serum. Insufficient blood volume may lead to test cancellation and jeopardise the statistical power. Hence, every effort must be done to collect blood volume as per protocol requirements.

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

Table 9 Biological samples

Sample type	Quantity	Unit	Timepoint	Subset name/ Group
Blood	~5	mL	Visit 3 (post-Dose 2)	All participants
Blood	~5	mL	Visit 4 (pre-Dose 3)	
Blood	~5	mL	Visit 5 (post-Dose 3)	

8.1.2. Laboratory assays

All laboratory testing will be performed at GSK laboratory or in a laboratory designated by GSK. Refer to Section 8.1.1 for details on blood sampling.

Immunogenicity of the vaccine against serogroups A, B, C, W and Y will be evaluated with the serum bactericidal assay using exogenous source of human complement (hSBA).

Table 10 Laboratory assays

CCI

Please refer to Section 10.2 for a brief description of the assays performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

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

CCI [redacted] ***(Amended, 28 Feb 2024)***

CCI [redacted]

8.1.4. Immunological correlates of protection

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

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

The immunological assay results will be communicated to the investigator when ready and available. Refer to Section 6.6 for details regarding treatment for non-responders.

8.2. Safety assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention or study.

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data *(Amended, 28 Feb 2024)*

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

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.2.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the parent(s)/LAR(s) and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

8.2.1.3. Physical examination

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

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

If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.5 for the list of criteria for temporary delay of study intervention administration.

Physical examination at each study visit after the first study intervention administration visit, will be performed only if the participant's parent/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

8.2.1.4. Warnings and precautions to administration of study intervention and non-study intervention

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention.

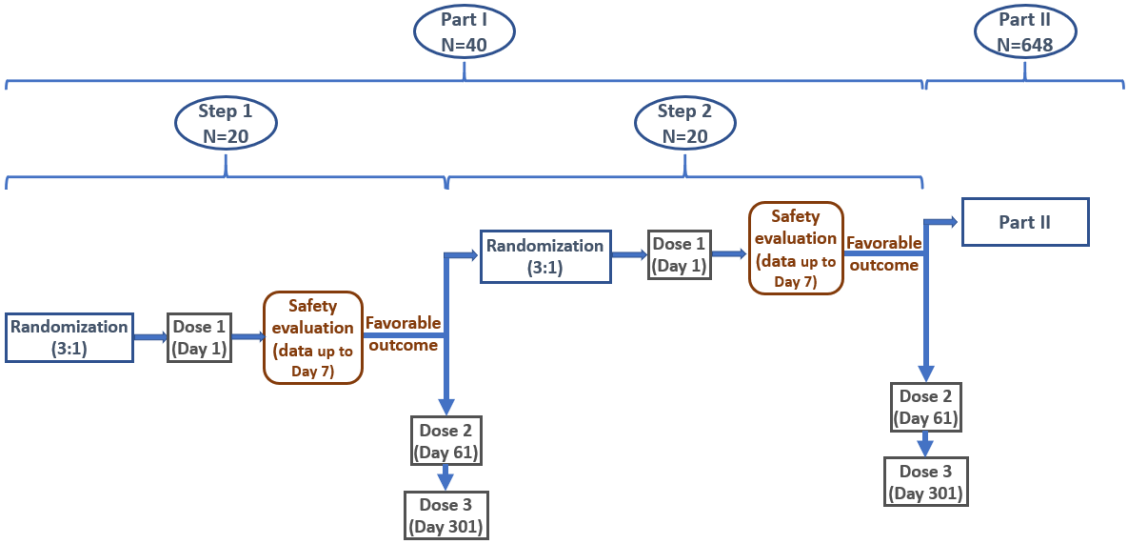
Refer to the IB of MenACWY-7B and MenABCWY vaccine and to the approved product label/package insert of *Bexsero, Nimenrix, Infanrix-Hexa, Prevenar 13* and *Rotarix.*

8.2.2. Study holding rules and safety monitoring

8.2.2.1. Staggered administration of study intervention

For Part I of the study, a staggered enrolment of healthy participants will be performed, as described in Figure 1 and Figure 2.

Figure 2 Stepwise approach for safety review in Part I



The following stepwise approach will be followed for the safety evaluation during the Part I:

- Step 1: Following the first vaccination in ACWY-7B[redacted] (15 participants) and MenB+MenACWY-TT (5 participants) groups solicited administration site and systemic events from all participants collected for 7 days, including the day of vaccination, and any AESIs and SAEs will be evaluated by the IDMC. The IDMC will be responsible for making a recommendation to the sponsor.
- Step 2: Following the first vaccination in ACWY-7B[redacted] (15 participants) and MenB+MenACWY-TT (5 participants) groups, solicited administration site and systemic events from all participants collected for 7 days, including the day of vaccination, and any AESIs and SAEs will be evaluated by the IDMC. The IDMC will be responsible for making a recommendation to the sponsor.

For both Step 1 and Step 2:

- If no safety signal is observed during the IDMC reviews, the favourable outcome of the safety evaluations will be documented and provided in writing to GSK with a recommendation to continue the study as planned (i.e. administer the subsequent dose of study intervention to participants and start the enrolment in the Step 2 or Part 2),
- If a safety signal is observed during the safety evaluations, the IDMC is responsible for the urgent communication to GSK, including the rationale for amending the protocol or suspending enrolment and/or intervention administration.

Details about the procedures to be followed in case of safety signal will be documented in the IDMC Charter.

Safety monitoring by the IDMC will be maintained throughout the study at additional predefined timepoints, as defined in the IDMC Charter. This will include solicited administration site and systemic events following subsequent vaccinations and all

unsolicited AEs, AESIs, and SAEs collected up to the predefined data lock point. Additional safety data may be reviewed and monitored by the IDMC whenever applicable.

Continuous safety monitoring during the study by the study team will allow for ad-hoc IDMC reviews and/or enrolment hold if any safety concern is identified or a substantial trend emerges outside of the scheduled unblinded safety reviews.

The proper composition and the details of all IDMC procedures will be documented in the IDMC Charter that will be provided as a separate document.

The investigator is not permitted to begin dosing study participants in Step 2 (Part I) and Part II or enrol additional participants until the receipt of written documentation of the favourable outcome of the IDMC safety evaluations, and written authorization to proceed.

8.2.2.2. Outcome of safety evaluation

If no safety signal is observed during the safety evaluations in Part I, the favourable outcome will be documented and provided in writing, authorising the investigator to start the administration of the subsequent dose of study intervention to participants, as well as enrolment and study intervention administration to the remaining participants in the next step of the study.

If a safety signal is observed during the safety evaluations or if any of the holding rules 2a-b is met, the IDMC Chair (or his/her representative) is responsible for the urgent communication to GSK, including the rationale for the recommendation to put the study intervention administration on hold or not. Details about the procedures to be followed in case of safety signal or if a holding rule 2 (a-b) is met will be documented in the IDMC Charter.

The study Clinical Research and Development Lead (CRDL) will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.

8.2.2.3. Study holding rules

Holding rules are defined to ensure well-controlled exposure to MenACWY-7B and MenABCWY vaccines and they will apply to study participants who have received any of the 2 investigational products in the study. The holding rules will hence serve as criteria to point attention to safety signals and require escalation within GSK, in order to decide whether other participants can be exposed. However, medical judgement considering all available safety data at the time of safety review should be the basis for decision to continue the study or not at each step.

The safety holding rules are defined in the Table 11 for Part I of the study and in Table 12 for Part II of the study.

Part I of the study

Holding rules 1a-d apply to Part I of the study and will be assessed by the investigator on a continuous basis. Meeting any of these holding rules will trigger a hold of study intervention administration irrespective of number of participants enrolled and/or timing of the event.

Holding rules 2a-b apply to Part I of the study and will be assessed by the IDMC during the safety evaluations on unblinded data.

Part II of the study

Holding rule 3 applies to Part II of the study and will be assessed by the investigator on a continuous basis: meeting this holding rule will trigger a hold of MenACWY-7B and MenABCWY vaccines' administration irrespective of number of participants enrolled and/or timing of the event.

These holding rules have been written under the assumption that the safety data from all participants will be available. If the data from all participants are not available (i.e. in case a participant is lost to follow-up), then the holding rules will be assessed on a pro-rata basis.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, missed visits due to study intervention related AEs, Grade 1 and Grade 2 solicited and unsolicited AEs in the 7-day follow-up period and unsolicited AEs collected from Day 8 to Day 30 after study intervention administration. However, if available, these data will also be reviewed by the IDMC to allow an overall assessment of the benefit/risk ratio of study intervention administration.

Table 11 Study holding rules *for Part I* of the study*

Holding rule	Event	Number or % of participants receiving the MenACWY-7B vaccine needed to trigger the hold
1a	Death or any life-threatening SAE regardless of causality	≥1
1b	Any non-life-threatening SAE that can be reasonably attributed to the vaccination	≥1
1c	Any withdrawal from the study (by investigator or participant request) following a Grade 3 AE that can be reasonably attributed to the vaccination	≥1
1d	Fever >40°C (104°F) OR any solicited administration site and/or systemic events leading to hospitalisation, OR necrosis at the injection site, each within the 7-day (Day 1-7) post-vaccination period	≥1
2a	Any Grade 3 solicited administration site event (lasting 48h or more) in the group, within the 7-day (Day 1-7) post-vaccination period	≥20%

Holding rule	Event	Number or % of participants receiving the MenACWY-7B vaccine needed to trigger the hold
2b	Any Grade 3 solicited systemic event (lasting 48h or more) within the 7-day (Day 1-7) post-injection period	≥20%

* The holding rules apply only to the participants that have received MenACWY-7B

Table 12 Study holding rules for Part II of the study*

Holding rule	Event	Number or % of participants receiving the MenACWY-7B or MenABCWY vaccine needed to trigger the hold
3	Any death (except death clearly not related to study interventions) or any life-threatening SAE reasonably attributed to the vaccination	≥1

* The holding rule applies only to the participants that have received MenACWY-7B or MenABCWY

If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study interventions (MenACWY-7B and MenABCWY) and inform GSK immediately (e.g. holding rules 1a-d or 3). Refer to Table 15 for contact information.

GSK will inform the investigator if holding rules 2a-b are met.

The following communication sequence must be followed:

- The concerned site staff must put the enrolment (all study arms) and the study interventions (MenACWY-7B and MenABCWY) administration on hold, while the administration of vaccines in the control arm (MenB+MenACWY-TT) can continue for the study participants previously enrolled.
- The concerned site staff must immediately inform their local contact defined in the Table 15.
- The LML will inform the other sites of his/her country, LMLs of other countries and the CRDL.
- All informed site staff will send back an email to their local contact to acknowledge receipt of the information.
- GSK Central will further evaluate the case with the external IDMC and will take the decision to stop or to restart the vaccination. CRDL who is the primary contact will inform the local GSK contact. All site staff will be informed about that final decision by their local GSK contact.

Where required per local/regional regulation, the central sponsor team submits a substantial amendment to the local/regional authority requesting authorization to restart the vaccination (administration of the next dose of the study vaccine or enrolment of additional participants).

When all required authorizations to restart the vaccination (administration of the next dose of the study vaccine or enrolment of additional participants) in a country / region have been provided, the central sponsor team provides written notification to local sponsor contacts; local sponsor contacts then provide written notification to study sites.

The investigator is not permitted to start the administration of the next dose or enrol additional participants until provided with written documentation of the favourable outcome of the safety evaluation, and written authorization to proceed.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

Table 13 Timeframes for collecting and reporting of safety information

Event	Pre-Dose*	Dose 1			Dose2			Dose 3			Study Conclusion
		D1	D7	D31	D61	D67	D91	D 301	D307	D331	D481
Administration site and systemic solicited events**											
Unsolicited AEs											
MAEs											
AEs/SAEs leading to withdrawal from the study											
SAEs											
SAEs related to study participation or concurrent GSK medication/ vaccine											
AESIs											

* i.e. consent obtained; D: Day, M: Month

** Solicited events that are ongoing after the 7-day reporting period may continue to be recorded in the eDiary until resolution or up to 30 days post-vaccination.

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.9. 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 periods defined in Table 13. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 15.

8.3.2. Method of detecting AEs and SAEs and other events

Detection and recording of AE/SAE/AESI are detailed in Section 10.3.7.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.8.

Open-ended and non-leading verbal questioning of participants' parent(s)/LAR(s) is the preferred method of acquiring information related to an AE/SAE/AESI.

8.3.3. Regulatory reporting requirements for SAEs and other events *(Amended, 28 Feb 2024)*

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/AESI, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 14. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.8.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of SUSAR must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/regulatory agencies about the safety of an investigational study intervention. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigators have to report to the sponsor medication errors, abuse and misuse even in an absence of an AE/SAE as these may be subjected to local regulatory reporting requirements for the sponsor.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Please refer to Section 10.3.9 for further details regarding the reporting of SAEs/AESIs.

Table 14 Timeframes for submitting SAE and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
AESIs	24 hours** ‡‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
** Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.
‡‡ The investigator will be required to confirm review of the SAE/AESI causality within 72 hours of submission of the SAE/AESI.

8.3.3.1. Contact information for reporting SAEs, AESIs and study holding rules

Table 15 Contact information for reporting SAEs, AESIs and study holding rules

Study contact for questions regarding SAEs, AESIs Refer to the local study contact information document	**Study contact for reporting of study holding rules** As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the LML.
Back up study contact for reporting SAEs, AESIs Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com Canadian sites only: Fax: 1 866 903 4718	**Back up study contact for escalation of holding rules**

8.3.4. Treatment of adverse events

Any medication administered for the treatment of an SAE/AESI should be recorded in the eCRF screen (refer to Section 10.3.9.1).

8.3.5. Participant card

The investigator (or designee) must provide the participant's parent(s)/LAR(s) with a "participant card" containing information about the clinical study. The participant's

parent(s)/LAR(s) must be instructed to always keep the participant card in his/her/their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/care giver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back up.

8.3.6. Medical device deficiencies

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

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

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

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6 for definitions and details on recording and reporting of these events.

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

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

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

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

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics

Not applicable.

8.6. Biomarkers

Not applicable.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

There are no statistical hypotheses to be tested. The study is descriptive.

9.2. Analysis sets

Table 16 Analysis sets

Analysis set	Description
Enrolled	Participants who were randomised or received study intervention.
Exposed	All participants who received at least 1 dose of the study intervention. Analysis per group using the Enrolled Set is based on the administered intervention. Safety analysis in this study will be assessed using the Exposed Set.
Full Analysis	All participants who received at least 1 dose of the study intervention and have post-vaccination immunogenicity data. The allocation in a group is done in function of the randomised intervention.
Per Protocol	All eligible participants who received all doses as per protocol, had immunogenicity results post-dose, complied with dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. The analysis will be done according to the study intervention that participants received at dose 1.

9.2.1. Criteria for elimination from analysis

If the participant meets one of the criteria listed in the Section 7.1.1, he/she may be eliminated from per protocol analysis.

9.3. Statistical analyses

9.3.1. Primary endpoints analysis

9.3.1.1. Safety and reactogenicity

Primary Endpoint	Statistical Analysis Methods
The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301.	Analysis set: Exposed Set Statistical methods: summarised descriptively, no testing will be performed
The frequencies and percentages of participants with any unsolicited AEs (including all MAEs, SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 301	Analysis set: Exposed Set Statistical methods: summarised descriptively, no testing will be performed
The frequencies and percentages of participants with MAEs, SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 481).	Analysis set: Exposed Set Statistical methods: summarised descriptively, no testing will be performed

9.3.1.2. Serogroup B indicator strains

Primary Endpoint	Statistical Analysis Methods
The percentages of participants with hSBA titre ≥LLOQ and summary statistics of hSBA titres and GMTs will be provided for each serogroup B indicator strain at 1 month after the second vaccination (Day 91), at pre-third vaccination (Day 301), and at 1 month after the third vaccination (Day 331). GMRs for each serogroup B indicator strain at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301) will also be presented.	**Analysis set:** Full Analysis Set **Statistical methods:** The percentages of participants with hSBA titre ≥LLOQ and the corresponding exact 2-sided 95% CIs based on the Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each serogroup B indicator strain. Difference between arms will be constructed with the method of Miettinen-Nurminen. For each serogroup B indicator strain 90% CIs for the GMTs ratio between ACWY-7B[CC1] / ACWY-7B[CC1] and MenB, will be created by exponentiating (base 10) the least squares means and the lower and upper limits of the 90% CIs of the log transformed titres (base 10) obtained from a 2-way Analysis of Variance (ANOVA) with factors for arms and centre. hSBA GMRs for each serogroup B indicator strain at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301) will be analysed similarly as the GMTs ratio, where the outcome in the model is the log transformed titre ratio of Day 331 versus Day 301. 90% CIs for the GMRs ratio between ACWY-7B[CC1] / ACWY-7B[CC1] and MenB, will be created by exponentiating (base 10) the least squares means and the lower and upper limits of the 90% CIs of the log transformed titres ratio (base 10) obtained from a 2-way ANOVA with factors for arms and centre.

9.3.1.3. Serogroups A, C, W and Y

Primary Endpoint	Statistical Analysis Methods
The percentages of participants with hSBA titre ≥LLOQ and summary statistics of hSBA titres and GMTs will be provided for each A, C, W and Y serogroup at 1 month after the second vaccination (Day 91), at pre-third vaccination (Day 301), and at 1 month after the third vaccination (Day 331). GMRs for each A, C, W and Y serogroup at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301) will also be presented.	**Analysis set:** Full Analysis Set **Statistical methods:** The percentages of participants with hSBA titre ≥LLOQ and the corresponding exact 2-sided 95% CIs based on the Clopper-Pearson method (Clopper and Pearson, 1934) will be calculated for each A, C, W, and Y serogroup. Difference between arms will be constructed with the method of Miettinen-Nurminen. For each A, C, W, and Y serogroup 90% CIs for the GMTs ratio between ACWY-7B[redacted]/ ACWY-7B[redacted] and MenACWY-TT, will be created by exponentiating (base 10) the least squares means and the lower and upper limits of the 90% CIs of the log transformed titres (base 10) obtained from a 2-way ANOVA with factors for arms and centre. hSBA GMRs for each A, C, W, and Y serogroup at 1 month after the third vaccination (Day 331) versus pre-third vaccination (Day 301) will be analysed similarly as the GMTs ratio, where the outcome in the model is the log transformed titre ratio of Day 331 versus Day 301. 90% Cis for the GMRs ratio between ACWY-7B[redacted]/ ACWY-7B[redacted] and MenACWY-TT, will be created by exponentiating (base 10) the least squares means and the lower and upper limits of the 90% CIs of the log transformed titres ratio (base 10) obtained from a 2-way ANOVA with factors for arms and centre.

9.4. Interim analyses *(Amended, 28 Feb 2024)*

An interim safety and immunogenicity analysis may be performed at 1 month after the second vaccination (Day 91). Furthermore, Part I data may be analysed separately. ***The interim analysis will be conducted such that the ongoing study integrity is maintained. Individual subject data and interim analysis results will not be shared with investigators nor participants before the final database lock. The study team will receive interim analysis results by treatment group only (no individual subject data). However, in limited instances (e.g., SAE experienced by a single participant throughout the study) treatment assignment may be revealed during the interim analysis, and the study will be considered single-blind for these participants from that point onwards, with the Investigator, site staff and participants remaining blinded up to final database lock.***

9.4.1. Sequence of analyses

A final study report will contain at least the final analyses of all endpoints.

9.4.2. Statistical considerations for interim analysis

There are no special statistical considerations for an interim analysis. In case an interim analysis will be performed, it will be performed when all participants completed the Visit 1 month after the second vaccination (Day 91), therefore only one comparison is made and not multiple, and therefore no adjustment is made in the 90% confidence level of the confidence intervals.

9.5. Sample size determination

The sample size determination was done to provide 90% CIs for the GMTs ratio between ACWY-7B[redacted]/ACWY-7B[redacted] and MenB+MenACWY-TT at 1 month post second dose, that have enough power to be greater than 0.5 for the endpoints related to serogroups A, C, W and Y and serogroup B indicator strains and greater than 1 for the endpoint related to serogroup B indicator strains for additional fHbp antigens.

Table 17 reads the assumptions for standard deviation (SD) and expected GMTs ratio, sample sizes, and power.

The assumptions made are:

- 85% evaluable participants of/in Part I
- all 205 enrolled participants in Part II before study hold are non-evaluable, and
- 85% evaluable participants in Part II after study restart with 443 participants to be enrolled.

[redacted]

Participants who withdraw from the study will not be replaced.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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.

10.1.2. 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.

10.1.3. Informed consent process

The investigator or his/her representative must fully explain the nature of the study to the participant's parent(s) or his/her LAR(s) and answer all questions regarding the study.

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

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

The content of the 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 centre.

The medical record must include a statement that written or witnessed/thumb printed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented if a new version of the ICF or an ICF addendum is released during their participation in the study.

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

10.1.4. Data protection *(Amended, 28 Feb 2024)*

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

The participants' parent(s)/LAR(s) must be informed that:

- Their child's personal study-related data will be used by the sponsor in accordance with local data protection law.
- Their child's medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

The participants' parent(s)/LAR(s) must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to

take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.5. Committees structure

10.1.5.1. Responsibilities of the Investigator and IRB/EC

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 [ICH, 1997]. A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

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

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

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

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

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

c. to the regulatory authority(ies).

10.1.5.2. Safety Review Committee

Refer to Section 8.2.2 for details.

10.1.6. Dissemination of clinical study data *(Amended, 28 Feb 2024)*

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within ***6*** months of primary/ study completion date ***(pediatric population) and within 12 months of primary/ study completion date (adult population).*** Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results***, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.***

Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymised patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. ***Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.***

10.1.7. Data quality assurance *(Amended, 28 Feb 2024)*

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

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

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

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (see ***DEFINITIONS OF TERMS*** for the exact definition of source documents) that supports information entered in the eCRF.

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

The sponsor or designee is responsible for the data management of this study including quality checking of the source data (see ***DEFINITIONS OF TERMS*** for the exact definition of source data).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorised site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g. via an audit trail). The safety and rights of participants must be protected, and the study 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 predefined in the Statistical Analysis Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These predefined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarised in the Clinical Study Report (CSR).

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever

is longer. 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. ***In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.***

10.1.8. Source documents

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any 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.

Definitions of what constitutes source data and documents can be found in the ***DEFINITIONS OF TERMS***.

10.1.9. Study and site start and closure

Start of study is defined as first subject first visit at a country-level.

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur 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 enough notice 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 participants by the investigator
- Discontinuation of further study intervention development

- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

At the end of the study, the investigator will:

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

10.1.10. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Immunogenicity laboratory assessments

The tests detailed in Table 10 will be performed at GSK or at a laboratory designated by GSK where the assays are available for the intended use.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

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

CCI



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[redacted]

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence (an unfavourable/unintended sign – including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. 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 administration of the study intervention even though they may have been present before study start. • Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits).
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. 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 participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF.
- Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that at any dose:	
a.	Results in death.
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c.	Requires hospitalisation or prolongation of existing hospitalisation Note: In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for

	observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
d.	Results in persistent or significant disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, 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.	Results in a congenital anomaly or birth defect in the offspring of a study participant.
f.	Other situations Medical or scientific judgement must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should 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; and convulsions that do not result in hospitalisation.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 18 Solicited administration site events

All age groups
Tenderness
Erythema
Induration
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 19 Solicited systemic events

Infant
Fever
Irritability/Fussiness
Loss of appetite
Drowsiness
Vomiting
Diarrhoea

Note: participants' parent(s)/LAR(s) will be instructed to measure and record the axillary temperature in the evening. If additional temperature measurements are taken at other times of the day, participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the eDiary card.

10.3.4. Unsolicited AEs

An unsolicited AEs is an adverse event that was not included in a list of solicited events using a Participant Diary. Unsolicited events must have been spontaneously communicated by a participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

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

Unsolicited AEs that are not medically attended or perceived as a concern by the participant's parent(s)/LAR(s) will be collected during an interview with the participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest (AESIs)

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

10.3.5.1. 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 20.

The investigator must exercise his/her medical/scientific judgement to determine whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD. In addition, the investigator should categorize each pIMD either as a new onset condition (if it started following vaccination) or as an exacerbation of a pre-existing chronic condition (if it exacerbated following vaccination) in the eCRF.

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

Table 20 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 anaemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anaemia • Autoimmune aplastic anaemia • 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.

10.3.5.2. Other adverse events of special interest

When there is enough evidence to make any of the below diagnoses, the AE must be reported as AESI**.** In addition, the investigator should categorize each AESI either as a new onset condition (if it started following vaccination) or as an exacerbation of a pre-existing chronic condition (if it exacerbated following vaccination) in the CRF/eCRF. Symptoms, signs or conditions which might (or might not) lead to one of the below diagnoses, should be recorded and reported as AEs but not as AESI until the final or definitive diagnosis has been made, and alternative diagnoses eliminated or shown to be less likely.

10.3.5.2.1. Febrile seizures

Seizures are defined according to the Brighton Collaboration Working Group case definition of generalised convulsive seizure as an adverse event following immunisation [Bonhoeffer, 2004].

The list of PTs corresponding to the diagnosis of seizure, are those included in the MedDRA Standard MedDRA Query (SMQ) Narrow "Generalised convulsive seizures following immunisation".

For any new diagnosis of generalised convulsive seizure (including febrile seizure), irrespective of seriousness, the investigator (or designate) must complete, an electronic Expedited Adverse Events Report and an ad-hoc eCRF page on seizures to further characterise this AESI.

10.3.5.2.2. Arthritis

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

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

  and/or

- Presence of diagnostic imaging studies interpreted by a health care provider as demonstrating evidence of joint inflammation and/or arthrocentesis results evidencing inflammation

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

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

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).

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

10.3.7. Recording and follow-up of AEs, SAEs and AESIs

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

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event, based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE instead of individual signs/symptoms.

An Electronic Diary (eDiary) will be used in this study to capture solicited administration site or systemic events. The participant parent(s)/LAR(s) should be trained on how and when to complete the eDiary.

Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record.

Verify completed eDiary during discussions with the participant's parent(s)/LAR(s) on Visit 2 (Day 61), Visit 3 (Day 91) and Visit 5 Day 331).

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

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

10.3.7.1. Time period for collecting and recording AEs, SAEs and AESIs

All post-study intervention immediate reactions observed within the observational period of at least 30 minutes after each injection, including signs or symptoms of anaphylaxis, allergic phenomena (such as rashes, itching, or other allergic manifestations), solicited events, unsolicited events and body temperature, will be recorded in the eCRF.

All solicited events that occur during 7 days following administration of each dose of study intervention (Day 1 to Day 7) must be recorded into the eDiary, irrespective of intensity. All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

Solicited events that are ongoing after the 7-day reporting period may continue to be recorded in the eDiary until resolution or up to 30 days post-vaccination (i.e., recording period for unsolicited AEs) whichever occurs first and do not need to be entered as an AE in the AE eCRF or the participant's source document. Any solicited event 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 participant's eCRF as an unsolicited AE. It will also be included in the participant's source documents at the site by the investigator/site staff as a verbally reported event. These events will be analysed as unsolicited AEs.

Any solicited event that meets any of the following criteria must also be entered into participants' source documents and as an AE on the AE eCRF:

- Solicited administration site or systemic events leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal).
- Solicited administration site or systemic events that otherwise meets the definition of SAE (see Section 10.3.2) or an AESI (See Section 10.3.5).

All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

Refer to Table 13 for the time period for collecting and recording unsolicited AEs, SAEs and AESIs.

10.3.7.2. Follow-up of AEs, SAEs, AESIs, or any other events of interest

After the initial AE/SAE/AESI or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

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

10.3.7.2.1. Follow-up during the study

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

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

10.3.7.2.2. Follow-up after the participant is discharged from the study

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

10.3.7.3. Updating of SAE and AESI information after removal of write access to the participant's eCRF

When additional SAE or AESI information is received after write access to the participant's eCRF is removed, 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 Section 8.3.3.1 or to GSK VCSP department within the defined reporting timeframes specified in the Table 14).

10.3.8. Assessment of intensity and toxicity

10.3.8.1. Assessment of intensity

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

Table 21 Intensity scales for solicited administration site events

Adverse Event	Grading of severity			
	Grade 0	Mild	Moderate	Severe
Tenderness	None	Minor reaction to touch	Cried or protested to touch	Cried when injected limb was moved
Erythema	0 mm	1 – 25 mm	26 – 50 mm	>50 mm
Induration				
Swelling				

Table 22 Intensity scales for solicited systemic events

Adverse Event	Grading of severity			
	Grade 0	Mild	Moderate	Severe
Irritability/Fussiness	None	Requires more cuddling and is less playful than usual	More difficult to settle	Unable to console
Loss of appetite	None	Eating less than normal for 1 – 2 feeds/ meals	Missed 1 or 2 feeds / meals	Missed more than 2 feeds/ meals
Drowsiness	None	Shows an increased drowsiness	Sleeps through feeds/ meals	Sleeps most of the time and it is hard to arouse him/her
Vomiting	None	1-2 times in 24 hours	3 – 5 times in 24 hours	6 or more times in 24 hours or requires intravenous hydration
Diarrhoea	Fewer than 2 loose stools in 24 hours	2 – 3 loose stools in 24 hours	4 – 5 loose stools in 24 hours	6 or more loose stools in 24 hours or requires intravenous hydration
Fever	<38.0°C (<100.4°F)	≥38.0 – 38.9°C (≥100.4 – 102.1°F)	≥39.0 – 39.9°C (≥102.2 – 103.9°F)	≥40.0°C (≥ 104.0°F)

* Refer to the SoA for the definition of fever and the preferred location for temperature measurement.

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

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

1 (mild) = An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities.

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the predefined outcomes as described in the Section 10.3.2.

10.3.8.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult

the IB and/or SmPC and/or Prescribing Information for marketed products to assist in making his/her assessment.

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

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

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

If an event meets the criteria to be determined 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

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

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

10.3.8.3. Medically attended visits

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

10.3.8.4. 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).

10.3.8.5. 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 World Health Organization (WHO) defined case definitions:

- Suspected COVID-19 case
- Probable COVID-19 case
- Confirmed COVID-19 case [WHO, 202*2*]

10.3.9. Reporting of SAEs, AESIs, and other events

10.3.9.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in enrolled participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 14 for the details on timeframes for reporting of SAEs/AESIs.

The investigator will be required to confirm the review of SAE causality within 72 hours of submission of the SAE.

Refer to Section 10.3.9.2 for information on back up systems in case the electronic reporting system does not work.

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

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (***refer to title page for details***) or to GSK VCSP department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

Not applicable.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

10.6.1. Definition of medical device AE and ADE

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavourable 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 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.

10.6.2. Definition of medical device SAE, SADE and USADE

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

10.6.3. 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.
- Email/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 8.3.3.1.
- GSK will review all device deficiencies, determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.7. Appendix 7: Country-specific requirements

10.7.1. Explanatory statement concerning Gender Distribution (Article 7, paragraph 2 (12) of the German GCP order)

There is no intention to conduct specific analyses investigating the relationship between the sex of the participants and the immunogenicity and safety of GSK's MenACWY-7B investigational vaccine. The ratio of male to female participants recruited into the study is expected to be in line with the demographics of the population aged 55 to 89 days of age in the Member state.

10.7.2. Recruitment/Randomisation agreement (only for UK sites)

For participants participating through home visits since Visit 1, the subject's parent(s)/LAR(s) will be requested to verbally consent the Recruitment/Randomisation agreement (RRA) to provide personal information and to agree to have their child randomised before providing written consent to participate in the study (to be provided at the first home visit).

The following information will be collected at centre level for participants for whom parent(s)/LAR(s) have verbally consented to the RRA to permit their randomisation/recruitment: age and contact information to allow future contact to book the vaccination visit(s). This information will be kept confidential at centre level.

The RRA is not a consent or confirmation of the subject's participation in the study. The RRA allows the sponsor/study staff to collect limited personal information about a subject whose parent(s)/LAR(s) have been contacted to let their child/ward participate in the clinical study. By agreeing to the RRA the subject's parent(s)/LAR(s) enables the study staff to allocate the subject to one of the study groups before providing informed consent. The first study-related activity/procedure other than the randomisation procedure can only be carried out after subject's parent(s)/LAR(s) have confirmed willingness to participate in the study and signed an ICF.

10.7.3. Study holding rules (only for UK sites)

Holding rules are defined to ensure well-controlled exposure to MenACWY-7B and MenABCWY vaccines and they will apply to study participants who have received any of the investigational products in the study. The holding rules will hence serve as criteria to point attention to safety signals and require escalation within GSK, in order to decide whether other participants can be exposed.

If any of the holding rules is met, the trial will be put on halt and it will be allowed to restart only after approval of a substantial amendment from the Medicines and Healthcare products Regulatory Agency (MHRA).

10.8. Appendix 9: 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
Protocol	04 June 2021
Protocol Amendment 1	01 September 2021
Protocol Amendment 2	18 February 2022
Protocol Amendment 3	31 October 2022
Protocol Amendment 4	28 Feb 2024

Amendments summary of changes table:

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol Amendment 1	01 September 2021	8.2.2. Study holding rules	Statement that, where required per local/regional regulation, in case of any holding rule is met, dosing will be paused and the trial can restart only after approval of a substantial amendment from the competent authorities, was added.	Medicines and Healthcare products Regulatory Agency (MHRA) requested to amend the protocol and state that if any of the holding rule is met dosing will be paused and the trial can restart only after approval of a substantial amendment from the competent authorities.
Protocol Amendment 2	18 February 2022	10.7.3. Study holding rules (Only for UK sites)	Statement included that in the UK, if one of the holding rules is met the trial can restart only after approval of a substantial amendment from the MHRA.	Medicines and Healthcare products Regulatory Agency (MHRA) requested a statement that the trial can restart only after approval of a substantial amendment from the MHRA if any of the holding rule is met.

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol Amendment 2	18 February 2022	8.2.2.3. Study holding rules and safety monitoring	Clarifications that the holding rules apply only to the study arms in which different formulations of MenACWY-7B will be tested and do not apply to the control arm (MenB+MenACWY-TT) were added.	Sponsor wants to clarify that the holding rules will apply only to the study arms which receive the primary study intervention.
		10.7.2. Recruitment/Randomisation agreement (only for UK sites)	Statement included that in the UK a verbal consent will be allowed when giving the recruitment/randomization consent.	To realign protocol wording with the local procedure in the UK where a verbal consent will be allowed when giving the recruitment/randomization consent as limited personal information will be required: age and contact information to allow future contact to book the vaccination visit(s). This information will be kept confidential at centre level.
		1.3. Schedule of activities	A note regarding the intercurrent medical condition in SoA was added.	The notes section was completed as per template.
		10.1.5. Committees structure	Committees structure section was added.	This section was missing in the protocol.

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol Amendment 2	18 February 2022	5.5 Criteria for temporarily delaying enrolment/randomisation/study intervention administration/ blood samples	Wording for participants with COVID-19 Criteria was changed.	The criteria was modified in order to allow countries to comply with local Covid regulations.
		10.3.2. Definition of an SAE	SAE definition was updated.	Italian Medicines Agency (AIFA) requested to update SAE definition.
		2.1. Study rationale	Further details about Phase I/II in adults and adolescents study were added.	The study started in June 2021, available safety data were added in the study rationale.
Protocol Amendment 3	31 October 2022	2.1. Study rationale	Updates were added on the status of the FTiH Phase I/II study currently ongoing with the investigational MenACWY-7B vaccine in adults and adolescents. The study vaccination and recruitment were temporary put on hold as a precautionary measure due to fatal events for which the causality has been investigated. Other study procedures (safety follow-up) continued as planned.	The updates reflect the enrolment status and the safety data available at the time of the amendment.

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol Amendment 3	31 October 2022	8.1.3. Immunological read-outs	The percentage of participants for each immunological test was revised.	Optimisation of MenACWY and MenB hSBA method allowed adjustments (decrease) of overall serum volumes required for hSBA clinical testing. As a consequence, all participants will be tested for immunogenicity against MenACWY, and immunogenicity subsets have been optimised for MenB immunogenicity.
		8.2.2.3. Study holding rules	Study holding rules were updated with regards to the investigational products exposure and study parts (Part I or Part II).	Holding rules are to apply for both investigational products. They were separated for the 2 parts of the study, with 1 new holding rule being added for Part II.
		9.4 Interim analyses	A new interim analysis previously not foreseen was added.	A separate analysis for Part I of the study is under consideration.
		9.5. Sample size determination	The number and percentages of evaluable participants were updated.	The assumptions, sample sizes and power were aligned with the immunological read-out test updates. The new assumption takes into account the participants that became non-evaluable during the study hold.

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol Amendment 3	31 October 2022	8.1.2. Laboratory assays 8.2.2.2. Outcome of safety evaluations	Other minor edits.	Edits applied for consistency or where minor updates were needed.

Detailed description of the current Protocol amendment:

Text that has been moved or added is presented in ***bold italics*** and deleted text in ~~strikethrough~~.

Protocol Amendment 3 Sponsor Signatory Approval page was deleted since the Sponsor approval will be obtained by e-signature.

Protocol sponsor information page was deleted, and the details were added in the title page of the protocol.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CTRIS:	***Center for Translation Research and Implementation Science***
Eu-CTR:	***European Clinical Trial Register***
IMP:	***Investigational medicinal product***

Term	Definition
AxMP	***Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.*** ***Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product.*** ***Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.*** ***Unauthoried AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004.*** ***Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.***
Caregiver	***A "caregiver" is someone who:*** • ***lives in the close surroundings of a participant and has a continuous caring role or*** • ***has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).*** ***In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.***
Co-administered product	***A product given to clinical trial participants as required in the protocol as part of their standard care for a condition that is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.***
Comparator	***Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is***

Term	Definition
	any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Decentralized trial platform	***A digital engagement technology allowing for the remote delivery and access to trials for participants, sites, and sponsors.***
eDiary	***Electronically recorded patient data and automated data entries on, for example, a handheld mobile device, tablet, or computer.***
HHS	***Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.***
Intercurrent event	***Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.***
Standard of care	***Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.***
SUSAR	***In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.***

Section 1.1. Synopsis

The **comparators** *Bexsero* (rMenB+OMV NZ, hereafter referred to as MenB) and *Nimenrix* (hereafter referred to as MenACWY-TT) will be administered as control vaccines.

Section 2.1. Study rationale

The iSRC recommendation was to continue the study with Phase II as planned, with ***1024*** participants aged 10 to 50 years ~~already~~ enrolled. At the time of finalization of this amendment, based on the safety data gathered from ~~more than~~ ***1024*** individuals aged 10 to 50 years in Phase II, no safety concerns were identified by the study Safety Review Team (SRT).

The present study is designed to evaluate the safety, tolerability and immunogenicity in healthy infants 2 months of age (MoA) at enrolment, of 2 MenACWY-7B vaccine formulations CCI and of the MenABCWY vaccine. ***The comparators*** *Bexsero* and *Nimenrix* will be administered as control vaccines.

The study vaccination and recruitment were temporary put on hold as a precautionary measure due to fatal events for which the causality has been investigated. Other study procedures (safety follow-up) continued as planned. The case reports demonstrated there is no causality between the fatal events and the investigational products (MenACWY-7B and MenABCWY). After the investigation ~~indicates~~***indicated*** a favourable benefit/risk assessment for the study participants, the study ~~will~~***was*** restart***ed*** with updated holding rules for Part II of the study (see Section 8.2.2).

Section 2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events of *Bexsero* (MenB) ***[Bexsero SmPC, 2017]****, Nimenrix* (MenACWY-TT) ***[Nimenrix SmPC, 2017]***, *Infanrix-Hexa* ***[Infanrix hexa SmPC, 2010]***, *Prevenar 13* ***[Prevenar 13 SmPC, 2014]*** and *Rotarix* ***[Rotarix SmPC, 2016]*** vaccines can be found in the Prescribing Information or Summary of Product Characteristics (SmPC).

Section 4.1. Overall design

Step 1:

- **ACWY-7B[redacted]**: Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT:** Participants will receive 3 doses of both ***comparators*** MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA, as control for the ACWY-7B[redacted] group.

Step 2:

- **ACWY-7B[redacted]:** Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT:** Participants will receive 3 doses of both ***comparators*** MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA, as control for the ACWY-7B[redacted] group.

Part II will start only after a positive outcome following IDMC review of the safety data from all participants receiving the first dose of both lower-dosage (MenACWY-7B[redacted]) and higher-dosage (MenACWY-7B[redacted]) vaccine formulations in Part I of the study (see Section 8 for details on IDMC reviews).

In Part II, ***approximately*** 648 eligible participants will be randomly assigned to 4 study groups in a 1:1:1:1 ratio:

- **ABCWY:** Participants will receive 3 doses of the ***investigational*** MenABCWY vaccine at 2, 4 and 12 MoA.
- **ACWY-7B[redacted]:** Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **ACWY-7B[redacted]:** Participants will receive 3 doses of the ***investigational*** MenACWY-7B[redacted] vaccine at 2, 4 and 12 MoA.
- **MenB+MenACWY-TT:** Participants will receive 3 doses of both ***comparators*** MenB and MenACWY-TT vaccines at 2, 4 and 12 MoA.

Control: ~~active comparator: MenB and MenACWY-TT vaccines will be administered as control at 2, 4 and 12 MoA~~ ***Men B and MenACWY-TT vaccines will be active comparators administered at 2,4 and 12 MoA***.

Section 4.4. End of Study Definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

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

End of Study (EoS): Date of the last testing/reading released of the Human Biological Samples ~~or imaging data~~, related to primary endpoints. EoS must be achieved no later than 8 months after Last Subject Last Visit (LSLV). ***If the completion of testing occurs prior the completion of the LSLV the latter date defines the*** ~~end of study visit~~ ***EoS.***

Note: The following non-study vaccines will be concomitantly administered as routine practice at study visits: *Infanrix-Hexa* and *Prevenar 13* at 2, 4, 12 MoA and *Rotarix* at 2 and 4 MoA. For more detailed information on study groups and treatments administered, refer to Table 4 and Table 5.

Duration of the study: The intended duration of the study, per participant, is approximately 16 months.

Control: ***Men B and MenACWY-TT vaccines will be active comparators administered at 2,4 and 12 MoA***.

Section 5. Study population

~~Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardise the scientific integrity, regulatory acceptability of the study or safety of the participant.~~***Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.***

Section 5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply: ~~All participants must satisfy ALL the following criteria at study entry:~~

- Participants' parent(s)/LAR(s) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the eDiaries, return for follow-up visits and is available for telephone calls). ***INC#1***
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the participant prior to performance of any study specific procedure. ***INC#2***
- Healthy participants as established by medical history and clinical examination before entering into the study. ***INC#3***
- A male or female between, and including, 55 and 89 days of age (approximately 2 MoA) at the time of the first study vaccination. ***INC#4***

- Born after a gestation period of ≥37 weeks, with a birth weight ≥2.5 kg. ***INC#5***

Section 5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. ***Participants are excluded from the study if any of the following criteria apply:*** ~~The potential participant MAY NOT be included in the study if ANY exclusion criterion applies:~~

Section 5.2.1. Medical conditions

- Current or previous, confirmed or suspected disease caused by *N. meningitidis*. ***EXC#1***
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection from birth. ***EXC#2***
- Progressive, unstable or uncontrolled clinical conditions. ***EXC#3***
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws. ***EXC#4***
- Any neuroinflammatory disorders (including but not limited to: demyelinating disorders, encephalitis or myelitis of any origin), congenital and peripartum neurological conditions, encephalopathies, seizures (including all subtypes such as: absence seizures, generalised tonic-clonic seizures, partial complex seizures, partial simple seizures or febrile convulsions). ***EXC#5***
- Congenital or peripartum disorders resulting in a chronic condition (including but not limited to chromosomal abnormalities, cerebral palsy, metabolism or synthesis disorders, cardiac disorders). ***EXC#6***
- Major congenital defects, as assessed by the investigator. ***EXC#7***
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s)/product(s). ***EXC#8***
- Hypersensitivity, including allergy, to any component of vaccines, including diphtheria toxoid (CRM_{197}) and latex medicinal products or medical equipment whose use is foreseen in this study. ***EXC#9***
- Abnormal function or modification of the immune system resulting from: ***EXC#10***
  - Autoimmune disorders (including, but not limited to: blood, endocrine, hepatic, muscular, nervous system or skin autoimmune disorders; lupus erythematosus and associated conditions; rheumatoid arthritis and associated conditions; scleroderma and associated disorders) or immunodeficiency syndromes (including, but not limited to: acquired immunodeficiency syndromes and primary immunodeficiency syndromes).
  - Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days starting from birth until Visit 5. This will mean prednisone equivalent ≥0.5 mg/kg/day with maximum 20 mg/day. Inhaled and topical steroids are allowed.

  - Administration of antineoplastic and immunomodulating agents or radiotherapy from birth.
  - Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study. ***EXC#11***

Section 5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccines from birth, or planned use during the study period. ***EXC#12***
- Previous vaccination with any meningococcal vaccine. ***EXC#13***
- Administration of immunoglobulins and/or any blood products or plasma derivatives from birth or planned administration during the study period until Visit 5. ***EXC#14***
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting from birth until Visit 5. For corticosteroids, this will mean prednisone equivalent ≥0.5 mg/kg/day with maximum 20 mg/day. Inhaled and topical steroids are allowed. ***EXC#15***

Section 5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device). ***EXC#16***

Section 5.2.4. Other exclusions

- Child in care (Please refer to the ***Definitions of terms*** ~~Glossary of terms~~ for the definition of child in care). ***EXC#17***
- Study personnel as an immediate family or household member. ***EXC#18***
- For contraindications to administering routine vaccines foreseen in the study (see Table 6), refer to their approved product label/package insert. ***EXC#19***

Section 6.1. Study interventions administered

The study interventions (refer to the ~~Glossary of terms~~ ***Definitions of terms*** for the definition of study intervention) will be provided by the sponsor.

Table 5 Study interventions administered

Study intervention *name*:	**MenACWY-7B[redacted][1]**		**MenACWY-7B[redacted][1]**		**MenABCWY[2]**		***Bexsero***	***Nimenrix***	
Study intervention formulation†	CCI [redacted]	MenA (10 µg) -CRM$_{197}$; MenC (5 µg) - CRM$_{197}$, MenW135 (5 µg)- CRM$_{197}$; MenY (5 µg)- CRM$_{197}$	CCI [redacted]	MenA (10 µg)- CRM$_{197}$; MenC (5 µg)- CRM$_{197}$; MenW135 (5 µg) - CRM$_{197}$; MenY (5 µg)- CRM$_{197}$	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHbp fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL[5]	MenA (10 µg)- CRM$_{197}$; MenC (5 µg)- CRM$_{197}$; MenW135 (5 µg)- CRM$_{197}$; MenY (5 µg)- CRM$_{197}$	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHbp fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL	MenA (5 µg)-TT; MenC (5 µg)-TT; MenY (5 µg)-TT; MenW-135 (5 µg)-TT	Sodium chloride; Water for ***injection*** q.s. 0.5 mL
Type	~~Study~~ ***Combination product***		~~Study~~ ***Combination product***		~~Study~~ ***Combination product***		~~Control~~ ***Combination product***	~~Control~~ ***Combination product***	
~~**Product category**~~	~~Combination product~~		~~Combination product~~		~~Combination product~~		~~Combination product~~	~~Combination product~~	
Use	***Investigational medicinal product***		***Investigational medicinal product***		***Investigational medicinal product***		***Comparator***	***Comparator***	
Authorized AxMP/	***Not applicable***		***Not applicable***		***Not applicable***		***Not applicable***	***Not applicable***	

Unauthorized AxMP					
Sourcing	***Provided centrally by the sponsor***				

Section 6.1.1. Non-study vaccines

~~The term 'non-study vaccine' refers to those vaccines which will be given to participants during the study but do not have associated study objectives. Non-study vaccines are Non-Investigational Medicinal Products and must be licensed in the country where they are administered.~~ The investigator is responsible for reporting AEs associated ***with co-administered vaccines*** ~~to the use of a non-study vaccine~~ according to local laws and regulations in addition to the safety reporting procedures foreseen in this study. The sponsor is responsible for the ongoing safety evaluation of the clinical trial participants including events related to ***co-administered vaccines*** ~~non-study vaccines~~.

The following ~~routine non-study vaccines~~ ***co-administered vaccines*** will be centrally supplied by the sponsor (see Table 6 for details) and will be ~~concomitantly~~ administered at study visits: *Infanrix-Hexa* and *Prevenar 13* at 2, 4, 12 MoA and *Rotarix* at 2 and 4 MoA. They will be recorded in the participants' eCRF.

Table 6 Concomitantly administered routine non-study vaccines

Study intervention *name*:	***Rotarix****	***Rotarix PCV-free****	***Prevenar 13***	***Infanrix-Hexa***	
Study intervention formulation †	HRV RIX4414 strain (≥$1\times10^{6.0}$ $CCID_{50}$); Sterile water q.s. 1.5 mL	HRV RIX4414 strain (≥$1\times10^{6.0}$ $CCID_{50}$); Sterile water q.s. 1.5 mL	PS1 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS3 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS4 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS5 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS6A (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS6B (4.4 µg)-CRM_{197} adsorbed on aluminium phosphate; PS7F (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS9V (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS14 (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS18C (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS19A (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS19F (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; PS23F (2.2 µg)-CRM_{197} adsorbed on aluminium phosphate; Aluminium phosphate (0.125 mg Al^{3+}); Water for injections q.s. 0.5 mL	DT (≥30 IU) adsorbed on aluminium hydroxide; TT (≥40 IU) adsorbed on aluminium hydroxide; PT (25 µg) adsorbed on aluminium hydroxide; FHA (25 µg) adsorbed on aluminium hydroxide; PRN (8 µg) adsorbed on aluminium hydroxide; HbsAg (10 µg) adsorbed on aluminium phosphate; IPV1 (Mahoney strain) (40 D-antigen units); IPV2 (MEF-1 strain) (8 D-antigen units); IPV3 (Saukett strain) (32 D-antigen units); Aluminium hydroxide ($Al(OH)_3$)/Aluminium phosphate ($AlPO_4$) (0.7 mg Al^{3+}); Water for injections q.s 0.5 mL	Hib (10 µg)-TT(~ 25 µg) adsorbed on aluminium phosphate; Aluminium phosphate
Type	~~Additional~~ ***Combination product***	~~Additional~~ ***Combination product***	~~Additional~~ ***Biologic product***	~~Additional~~ ***Combination product***	
~~**Product category**~~	~~Combination product~~	~~Combination product~~	~~Biologic product~~	~~Combination product~~	
Use	***Co-administered product***	***Co-administered product***	***Co-administered product***	***Co-administered product***	
Authorized AxMP/ Unauthorized AxMP	***Authorized AxMP***	***Authorized AxMP***	***Authorized AxMP***	***Authorized AxMP***	
Sourcing	***Provided centrally by the sponsor***				

Section 8. STUDY ASSESSMENTS AND PROCEDURES

Decentralised study procedures

Following procedures can be performed remotely/virtually. Refer to the ~~Glossary of terms~~ ***Definitions of terms*** for the definitions of telemedicine, remote and virtual visits:

CCI

[redacted]

Section 8.2.1.1. Collection of demographic data

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

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

Section 8.3.3. Regulatory reporting requirements for SAEs and other events

Investigators have to report to the sponsor medication errors, abuse and misuse even in an absence of an AE/SAE as these may be subjected to local regulatory reporting requirements for the sponsor.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Section 8.3.6. Medical device deficiencies

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~~ ***Definitions of terms*** for the definition of combination product and medical device deficiency.

Section 9.4. Interim analyses

An interim safety and immunogenicity analysis may be performed at 1 month after the second vaccination (Day 91). Furthermore, Part I data may be analysed separately. ***The interim analysis will be conducted such that the ongoing study integrity is maintained. Individual subject data and interim analysis results will not be shared with investigators nor participants before the final database lock. The study team will***

receive interim analysis results by treatment group only (no individual subject data). However, in limited instances (e.g., SAE experienced by a single participant throughout the study) treatment assignment may be revealed during the interim analysis, and the study will be considered single-blind for these participants from that point onwards, with the Investigator, site staff and participants remaining blinded up to final database lock.

Section 9.5. Sample size determination

CCI



Section 10.1.4. Data protection

GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

Section 10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within ***6*** months of primary/ study completion date ***(pediatric population) and within 12 months of primary/ study completion date (adult population).*** Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results***, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.*** ~~The investigator is encouraged to share the summary results with the study participants, as appropriate.~~

Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymised patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. ***Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.***

Section 10.1.7. Data quality assurance

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

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

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

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

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

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever is longer. ~~Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance 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. ***In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.***

Section 10.1.8. Source documents

Definitions of what constitutes source data and documents can be found in the ~~Glossary of terms~~***Definitions of terms***.

Section 10.3.9.2. Back up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (~~refer to Sponsor Information~~ ***refer to title page for details***) or to GSK VCSP department within 24 hours of becoming aware of the SAE.

Section 11. References

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