CLINICAL STUDY PROTOCOL

Primary study intervention(s)	rMenB+OMV NZ
Other study intervention(s)	Not applicable
Study identifier	220030
Abbreviated title	MENB REC 2ND GEN-096 BST:002,055,058
EU CT number	2024-519549-31
Approval date	29 Aug 2025
Title	A Phase 3b, open-label, multi-center study to assess the immune response and safety of the meningococcal group B vaccine rMenB+OMV NZ when administered to healthy participants aged 10 to 20 years old, who were primed during the first 2 years of life
Brief title	A Phase 3 study to assess the immune response and safety of rMenB+OMV NZ in primed healthy participants (10 to 20 years old)
Sponsor	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Pavitra Keshavan Senior Director, Clinical Project Lead

Site-specific contact of GSK (or GSK-delegate) name and contact information can be found in the local study contact information document.

Based on TMF-14732712 Protocol v4.0.

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Protocol Amendment 1 Investigator Agreement

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with Good clinical practices (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	220030
Abbreviated title	MENB REC 2ND GEN-096 BST:002,055,058
EU CT number	2024-519549-31
Approval date	29 Aug 2025
Title	
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	29 Aug 2025
Amendment EU-1	16 July 2025
Original Protocol (Version 1)	20 January 2025

Amendment 1 (29 Aug 2025)

Overall rationale for the current Amendment: This is a substantial global amendment in response to Medicines and Healthcare products Regulatory Agency (MHRA) feedback to clarify eligibility criteria related to childbearing potential and contraception and European Union Clinical Trials Regulation (EU CTR) feedback to specify the procedure for reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database. Also, the protocol is updated to align with latest GSK template.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
LIST OF ABBREVIATIONS AND DEFINITIONS	Added EU CTR – European Union Clinical Trials Regulation	To introduce and define all abbreviations.
1.1 Synopsis	The Section was added on data monitoring and statistical analysis sections.	To align with the updated GSK template.
4.2.1 Participant input into design	The Section was added on participant input into design.	To comply with EU CTR requirements.
5.1 Inclusion Criteria Inclusion Criterion 4	The note was updated with 'or as per local country regulations' for clarification.	To comply with EU CTR requirements.
5.1 Inclusion Criteria Inclusion Criterion 6	Deleted "current bilateral tubal ligation or occlusion" from definition of females of non-childbearing potential.	To comply with MHRA requirement.
5.3 Lifestyle considerations	The Section was added to describe lifestyle considerations.	To align with the updated GSK template.
8.4.5 Regulatory reporting requirements for SAEs/AESIs	The section was updated to include information about Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting.	To comply with EU CTR requirements.
10.7 Appendix 7 Country-specific requirements	The Section was added to align protocol with EU CTR.	To comply with EU CTR requirements.
10.9 Appendix 9: Protocol deviations	The Section was added to describe protocol deviations recording.	To align with the updated GSK template.
Throughout the protocol	Clarification and definitions updated throughout the document as per updated GSK template.	To align with the updated GSK template.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	Adverse device effect
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AxMP	Auxiliary medicinal product
CA	Competent authority
CFR	Code of Federal Regulations
CONSORT	Consolidated standards of reporting trials
CSR	Clinical study report
CTA	Clinical trials application
ECG	Electrocardiogram
eCRF	electronic Case report form
eDiary	electronic Diary
EoS	End-of-study
EU CTR	European Union Clinical Trials Regulation
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GCP	Good clinical practices
HRT	Hormonal replacement therapy
IAF	Informed assent form
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICSR	Individual case safety reports
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
LAR	Legally acceptable representative
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PI	Personal information
PK	Pharmacokinetics
QTL	Quality tolerance limit
rDNA	recombinant Deoxyribonucleic acid
rMenB+OMV NZ	Recombinant Meningococcal B with Outer Membrane Vesicle derived from *Neisseria meningitidis* serogroup B strain NZ98/254 (New Zealand strain) Vaccine (*Bexsero*)
RTMS	Randomization and Trial Supply Management
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Definition
SmPC	Summary of product characteristics
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TOC	Table of contents
ULN	Upper limit of normal
USADE	Unanticipated serious adverse device effect
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Term	Definition
AxMP	Medicinal products used in the context of a clinical trial but not as Investigational medicinal product (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 Suspected unexpected serious adverse reaction (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.
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.
Challenge agent	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.

Term	Definition
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.
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).
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.
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.
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.
Intervention number	A number identifying the intervention assigned to a participant, according to intervention allocation.
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).
Non-IMP	Any products used in a clinical trial (other than the investigational product being tested) which are stipulated to be used to evaluate the efficacy and safety of the investigational drug in the protocol including comparators, co-administration drugs, rescue drugs and premedication drugs. • Non-IMPs products can be approved in Japan or other countries, or can be products that are not approved.
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.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.

Term	Definition
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.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Rescue medication	Medicine(s) identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the participant, or to manage an emergency situation.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
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.
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.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A Phase 3b, open-label, multi-center study to assess the immune response and safety of the meningococcal group B vaccine rMenB+OMV NZ when administered to healthy participants aged 10 to 20 years old, who were primed during the first 2 years of life

Brief title: A Phase 3 study to assess the immune response and safety of rMenB+OMV NZ in primed healthy participants (10 to 20 years old)

Rationale: *Neisseria meningitidis* (*N. meningitidis*) infections, leading to invasive meningococcal disease (IMD), are a significant global health issue due to their high morbidity, mortality, and transmissibility. The serogroup B (MenB) strain is particularly prevalent in North America and Europe, with the highest rates of disease found in infants, young children, and adolescents. The rMenB+OMV NZ vaccine, also known as Bexsero, is used for active immunization against MenB in individuals aged 2 months and older and is approved in over 55 countries. However, concerns exist about the waning immunity of the vaccine in infants and toddlers, potentially leaving adolescents unprotected during the additional peak of MenB disease. The study aims to assess the immune response to a booster dose of rMenB+OMV NZ in individuals aged 10 to 20 years who were initially vaccinated as infants, compared to one dose in those who have never received a group B meningococcal vaccine. For more details on the study rationale, refer to Section 2.1.

Objectives, endpoints, and estimands: The primary objective of this study is to demonstrate the superiority of the immune response to one booster dose of rMenB+OMV NZ in the primed group, compared to the first dose in naïve group against each MenB indicator strain. The primary endpoint measures the ratio of GMT against each MenB indicator strain in the primed and the naïve group. The secondary objectives are: (1) to evaluate the humoral immune response to one booster dose of rMenB+OMV NZ in the primed group, and first dose of rMenB+OMV NZ in the naïve group; (2) to evaluate the bactericidal activity at baseline in the primed group and in the naïve group; and (3) to evaluate the safety of rMenB+OMV NZ throughout the study period. For more details on objectives, endpoints and estimands, refer to Section 3.

Overall design: This is a Phase 3b, open-label, multi-center study to assess the immune response and safety of a single booster dose of rMenB+OMV NZ when administered to healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in a 2+1 or 3+1 schedule during the first 2 years of life in comparison to the first dose in naïve subjects.

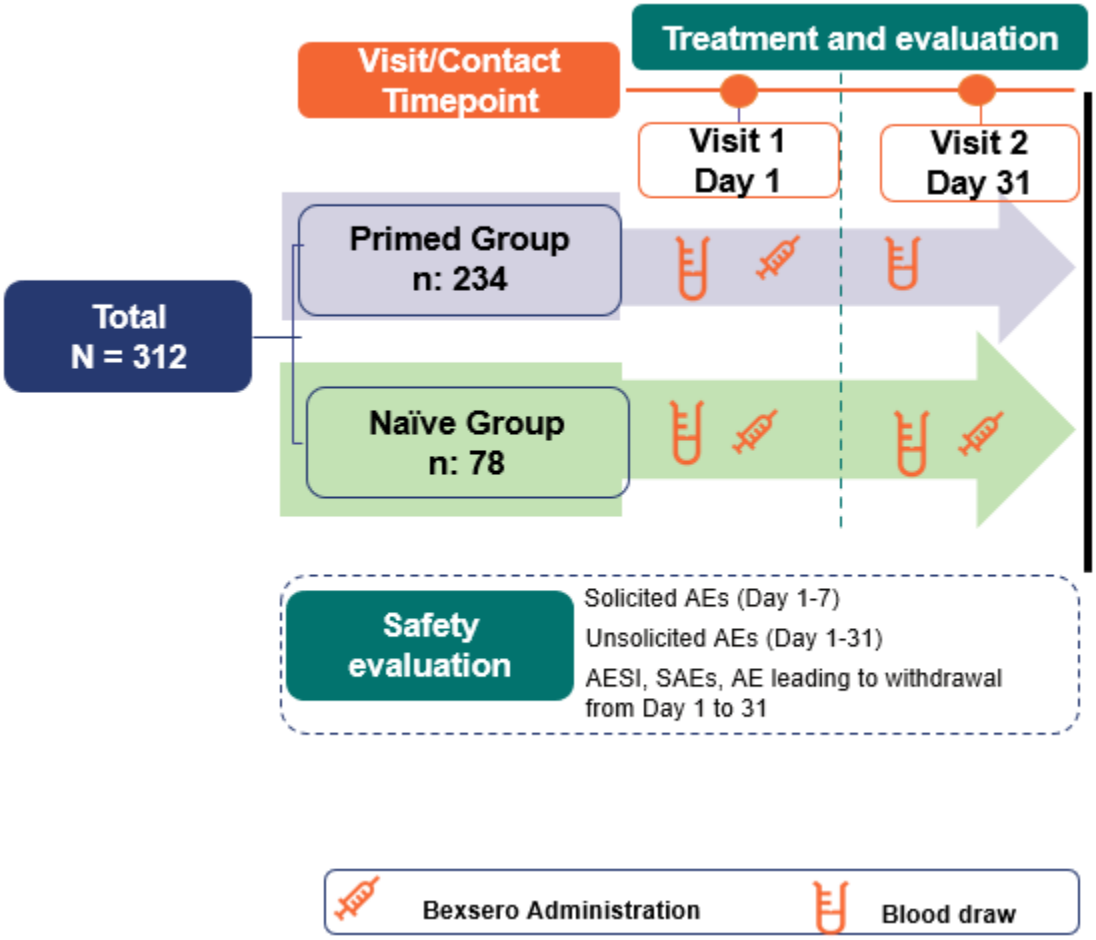
Number of participants: With an assumed 10% of non-evaluable participants and a 3:1 participant ratio between groups, the number of participants to be enrolled will be 312, of which, 234 will be in the primed group and 78 in the naïve group. For more details, refer to Section 9.5.

Data monitoring/other committee: No data monitoring committee has been established for this study.

Statistical Analysis: For the primary objective of the study, ANOVA will be applied to log-transformed hSBA titers to calculate GMTs for both groups, with superiority established if the lower limit of the two-sided 95% confidence interval for the GMT ratio exceeds 1. The primary and subgroup analyses based on age will be conducted on the Full Analysis Set, while a sensitivity analysis using a causal inference method will address the non-randomized nature of the study. For more details, refer Section 9.

1.2. Schema

Figure 1 Study design overview



Abbreviations: AESI = Adverse event of special interest; N/n = Number of participants; (S)AE = (Serious) Adverse event.

1.3. Schedule of activities

Table 1 Schedule of activities

Type of contact Timepoint(s)	Visit 1 Day 1	Visit 2 Day 31 (Allowed interval: Day 28 – Day 38)	Notes
Informed consent	●		See Section 10.1.3 for details.
Inclusion and exclusion criteria	●		See Section 5.1 and Section 5.2 for Inclusion and Exclusion criteria.
Demography	●		See Section 8.1.1 for more information.
Medical history	●		See Section 8.1.2 for more information.
History of Meningococal B vaccination†	●		See Section 8.1.2 for more information.
History of MenACWY vaccines	●		See Section 8.1.2 for more information.
History directed physical examination	○		See Section 8.3.1 for more information.
Symptom directed physical examination		○*	
Study Intervention			
Check contraindications, warnings, and precautions to study intervention administration	○	○*	See Section 7.1.1 for more information.
Check criteria for temporary delay for enrollment and/or study intervention administration/blood draw	○	○	See Section 5.5 for more information.
Urine pregnancy test[a]	●	●*	See Section 8.3.3 for more information.
Intervention number allocation	○		See Section 6.3 for more information.
Intervention number allocation for subsequent dose		○*	
Body temperature before study intervention administration[b]	●	●*	The preferred location for measuring temperature will be axilla
Administration of study intervention	●	●*	See Section 6.1 for more information.
Recording of administered study intervention number	●	●*	
Post-injection assessment (30 minutes)	●	●*	
Distribution/Set-up of eDiaries	○		See Section 10.3.5.1 for more information.
Laboratory assessment			
Blood sampling for antibody determination (approximately 20 mL at each visit)	●[c]	●[c]	See Section 8.2.2 for more information.
Safety assessments			
Record concomitant medications/vaccinations	●	●	See Section 6.9 for more information.

Type of contact Timepoint(s)	Visit 1 Day 1	Visit 2 Day 31 (Allowed interval: Day 28 – Day 38)	Notes
Record intercurrent events/medical conditions	●	●	See Section 6.9 for more information.
Recording of solicited AEs within 7 days (including the day of injection) post vaccination at Day 1	●		See Section 10.3.5 for more information. Follow-up until resolution for events ongoing at the solicited period (Days 1-7).
Recording of unsolicited AEs within 31 days (including the day of injection) post vaccination at Day 1	●	●[e]	See Section 10.3.5 for more information.
Recording of AESI[d], SAEs, AEs leading to withdrawal	●	●	See Section 10.3.5 for more information.
Recording of SAEs related to study participation or concurrent GSK medication/vaccine	●	●	See Section 10.3.5 for more information.
Review of eDiaries		○	The study staff should review that participant or parent/LAR has captured the information in the eDiaries before the eDiaries are returned/uninstalled.
Return/Uninstall of eDiaries[f]		○	
Study conclusion		●	

Abbreviations: AE = Adverse event; AESI = Adverse event of special interest; eDiary = electronic Diary; GSK = GlaxoSmithKline Biologicals SA; LAR = Legally acceptable representative; SAE = Serious adverse event.

● Is used to indicate a study procedure that requires documentation in the individual eCRF.

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

* For naïve group only.

† Refers to any Meningococcal B vaccines, not only Bexsero.

a. Urine pregnancy test will be performed prior to study intervention administration, only for female participants of childbearing potential.

b. Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature will be axillary. If any other route is used for measuring temperature, this needs to be recorded in the eCRF.

c. Blood sampling will be performed before study intervention administration.

d. AESI: arthritis.

e. The last day of unsolicited AE collection is Day 31 regardless of the delay of the visit.

f. For those who used site-provided eDiary devices, the eDiary device must be returned. For those who install the eDiary study application into their personal mobile devices, this application must be uninstalled.

2. INTRODUCTION

2.1. Study rationale

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. *N. meningitidis* serogroup B (MenB) accounts for a high proportion of meningococcal cases in North America and Europe, with a case-fatality ratio ranging from 3% to 10% [Sridhar, 2015]. The rate of serogroup B disease is highest in infants, followed by 1 to 4-year-olds, with a third peak in adolescents [ECDC, 2022; CDC, 2018].

rMenB+OMV NZ (also referred to as *Bexsero*) vaccine is indicated for active immunization against IMD caused by MenB for individuals aged 2 months and older, with some differences in the age group indication depending on the country where the vaccine is registered. rMenB+OMV NZ was registered first in the European Union in 2013 and is currently approved in more than 55 countries worldwide and is included in many national immunization programs (NIP) of infants (e.g. Australia, United Kingdom, Ireland, France, Germany, Italy, San Marino, Malta, Andorra, Lithuania, Luxembourg, Portugal, Czech Republic, Spain, Switzerland, Chile, New Zealand and Greece).

Due to waning of immunity, the rMenB+OMV NZ vaccine given in infants and toddlers might not provide sufficient protection for adolescents, at the age when the additional peak of MenB disease is observed [Snape, 2013; McQuaid, 2015; Martinón-Torres, 2018]. Furthermore, since rMenB+OMV NZ is increasingly included in the infant NIP, the timing, dosage and need for a booster dose in individuals primed as infants needs to be determined.

The main purpose of this study is to evaluate the immune response (or booster ability) to a single booster dose of rMenB+OMV NZ when it is given at 10 to 20 years of age to those who received infant schedule (primed group) when compared with those who never received any group B meningococcal vaccine (naïve group) after one dose of rMenB+OMV NZ vaccine administration.

2.2. Background

N. meningitidis is the 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. Symptoms of IMD occur rapidly and often result in severe outcomes within a few hours. Despite the availability of medical treatment and effective antibiotics for IMD, 8% to 15% of patients die, with case-fatality rates increasing with age [ECDC, 2022; Cohn, 2013]. Of those that survive the infection, 10% to 20% have long-term sequelae, including disability, limb amputation, and deafness [Mbaeyi, 2020].

Over 90% of meningococcal meningitis and septicemia are caused by 5 of the 13 meningococcal serogroups, i.e., serogroups A, B, C, W, and Y [Girard, 2006]. Serogroup B accounts for a high proportion of meningococcal cases in North America and Europe, with a case-fatality ratio ranging from 3% to 10% [Sridhar, 2015]. Age-specific rates were highest in infants aged less than 1 year, followed by 1 to 4 years old and 15 to 24 years old [ECDC, 2022].

Capsular polysaccharide vaccines have been used successfully in preventing disease and limiting epidemics and outbreaks caused by meningococcal serogroups A, C, W135, and Y. However, the capsular polysaccharide of serogroup B is poorly immunogenic in humans, possibly due to the antigenic similarities in serogroup B carbohydrate moieties to carbohydrates distributed in the human body. As a result, research has focused on proteins in the outer membrane of meningococci as potential antigens for candidate vaccines. Serogroup B vaccines based on protein-containing outer membrane vesicles (OMV) have shown to be safe and effective in controlling the epidemic disease caused by strains homologous to the vaccine strain in Cuba, Brazil, Chile, Norway, and New Zealand. However, the use of these OMV vaccines to combat serogroup B meningococcal disease have been limited due to the strain-specific nature of the protection and the lack of consistent efficacy in young children.

GSK's serogroup B meningococcal vaccine, *Bexsero* (hereafter referred to as rMenB+OMV NZ) is developed based on the knowledge gained during the vaccine development for the Norwegian (MenBvac) and New Zealand (MeNZB) epidemics, along with the identification of the *N. meningitidis* serogroup B genome sequence [Kelly, 2007; Galloway, 2009]. The availability of the bacterial genome sequence allowed identification of conserved surface-exposed outer membrane proteins of serogroup B strains that were targets for bactericidal antibodies [Pizza, 2000]. rMenB+OMV NZ is based on 3 proteins: i) Factor H binding-protein (fHbp), ii) Neisseria adhesin A (NadA), and iii) Neisseria Heparin Binding Antigen (NHBA) or 287. To increase the potency of the immune response, fHbp has been combined with the accessory protein GNA2091 (936), and NHBA has been combined with GNA1030 (953), to create 2 fusion proteins.

rMenB+OMV NZ is indicated for active immunization against invasive disease caused by *N. meningitidis* serogroup B for individuals aged 2 months and older, with some differences in the age group indication depending on the country where the vaccine is registered. rMenB+OMV NZ was registered first in the European Union in 2013 and is currently approved in more than 55 countries and regions worldwide, including the United States (US).

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

2.3. Benefit-risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events of rMenB+OMV NZ vaccine can be found in the 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 participants with an immediate systemic allergic reaction to vaccination, all participants will need to remain under close observation for at least 30 minutes after each study intervention.

2.3.1. Risk assessment

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Study intervention(s)		
Important potential risk **Arthritis**	Attenuated live virus vaccines (rubella) were reported to be associated with joint-related diseases [Tingle, 1986]. Among inactivated vaccines, different manifestations of arthritis following hepatitis B vaccination (psoriatic arthritis, reactive arthritis, etc.) were described [IOM, 2011] however, no association with meningococcal vaccines has been reported in the literature. This important potential risk derived from a signal detected for Bexsero. One clinical case of juvenile idiopathic arthritis (JIA) was considered to be possibly related to Bexsero by the Company. Further details regarding this case are provided in the IB.	Arthritis will be monitored through the AESI collection (refer Section 8.4.4).
Study procedures		
Risk of blood sampling	Blood sampling is associated with a risk of local reactions and infection after or during venipuncture	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the health of the participant.

Abbreviations: AESI = Adverse event of special interest; ICF = Informed Consent Form.

2.3.2. Benefit assessment

Receiving rMenB+OMV NZ during study may protect participants against meningococcal B disease.

2.3.3. Overall benefit-risk conclusion

Taking into consideration the measures taken to minimize risk to participants from this study, the potential risks identified in association with rMenB+OMV NZ are justified by the anticipated benefits (prevention) that may be afforded to participants receiving this vaccine.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 2 Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the superiority of the immune response to one booster dose of rMenB+OMV NZ in the primed group*, compared to the first dose in naïve group† against each MenB indicator strain.	• hSBA titers against each MenB indicator strain at Visit 2 (Day 31).
Secondary	
To evaluate the humoral immune response to one booster dose of rMenB+OMV NZ in the primed group*, and first dose of rMenB+OMV NZ in the naïve group†.	• hSBA titers against each MenB indicator strain at Visit 2 (Day 31).
To evaluate the bactericidal activity at baseline in the primed group* and in the naïve group†.	• hSBA titers against each MenB indicator strain at Visit 1 (Day 1).
To evaluate the safety of rMenB+OMV NZ throughout the study period.	• Occurrence of solicited administration site and systemic events within 7 days following the first vaccination. • Occurrence of any unsolicited AEs within 31 days (including the day of injection) following the first vaccination. • Occurrence of AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period (Day 1 to Day 31).
Exploratory	
To evaluate the bactericidal activity at baseline and to evaluate the humoral immune response against serotype A, C, W and Y to 1 dose of rMenB + OMV NZ in the primed group* and in the naïve group†	• hSBA titers against each ACWY serogroup at Visit 1 (Day 1) and at Visit 2 (Day 31).

Abbreviations: AE: Adverse event; AESI: adverse event of special interest; hSBA: human serum bactericidal assay; MenB: meningococcal bacteria belonging to N. meningitis serogroup B; rMenB+OMV NZ: recombinant Meningococcal B with Outer Membrane Vesicle derived from *Neisseria meningitidis* serogroup B strain NZ98/254 (New Zealand strain) Vaccine (*Bexsero*); SAE: Serious adverse event.

*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life.

† Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

** Four-fold increase (seroconversion) defined as:

- Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2;
- Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥ 2.

PRIMARY ESTIMAND

Table 3 Study estimand - primary objective

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Primary Estimand: Superiority of the immune response to one booster dose in the primed group* compared to the first dose in the naïve group†.						
Clinical question of interest: The interest lies in demonstrating the superiority of the immune response to a single booster dose of rMenB + OMV NZ in the primed group compared to the first dose in naïve group against each MenB indicator strain, regardless of ICEs occurrence. A supportive analysis will also be conducted to address the instance in which ICEs had never occurred. **Rationale:** As the interest is in evaluating the superiority of the immune response to one booster dose compared to the first dose in naïve participants, in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used. A supportive analysis is conducted using the hypothetical strategy to evaluate the superiority of the immune response to one booster dose compared to the first dose in naïve participants, in a setting where participants would adhere to the protocol requirements.						
Primary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each MenB indicator strain in primed and naïve group at Visit 2 (Day 31)	• Blood draws occurring outside the protocol-defined visit window. • Errors in first/booster dose vaccine administration: o Vaccine temperature excursion o Expired vaccine o Lower volume of vaccine o Other errors lead to vaccine not administered according to the protocol • Administration of a vaccination forbidden by the protocol. • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for the primary immunogenicity endpoint, i.e., the value of the endpoint is used regardless of whether or not the intercurrent event occurs. The hypothetical strategy will be used for the supportive analysis, i.e. ICE will be handled as it had never occurred, data post ICE will not be considered for the analysis of the outcome measure.	• Ratio of GMTs against each MenB indicator strain between the primed and naive group at visit 2 (Day 31).
Abbreviations: GMT: geometric mean titer; hSBA: human serum bactericidal assay; MenB: meningococcal bacteria belonging to N. meningitis serogroup B. *Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life. † Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.						

SECONDARY ESTIMANDS

Table 4 Study estimands - secondary objectives

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Secondary Estimand: Immunogenicity of one booster dose in the primed group*, and first dose in the naïve group†						
Clinical question of interest: The interest lies in assess the immune response to a single booster dose of rMenB+OMV NZ in the primed group* and the first dose in the naïve group† against each MenB indicator strain, regardless of ICEs occurrence. **Rationale:** As the interest is in evaluating the immune response to one booster dose in the primed group and to the first dose in naïve group in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used.						
Secondary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each MenB indicator strain at Visit 2 (Day 31)	• Blood draws occurring outside the protocol-defined visit window. • Errors in first/booster dose vaccine administration: ○ Vaccine temperature excursion ○ Expired vaccine ○ Lower volume of vaccine ○ Other errors lead to vaccine not administered according to the protocol. • Administration of a vaccination forbidden by the protocol. • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for immunogenicity endpoints, i.e., the value for each of the endpoints is used regardless of whether or not the intercurrent event occurs	• Number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each MenB indicator strain at Visit 2 (Day 31). • Number and percentage of participants with hSBA titers ≥LLOQ against each MenB indicator strain at Visit 2 (Day 31). • Number and percentage of participants with four-fold increase** in hSBA titers at Visit 2 (Day 31) relative to Visit 1 (Day 1). • hSBA GMTs and GMRs at Visit 2 (Day 31) compared to Visit 1 (Day 1) against each MenB indicator strain.

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Secondary Estimand: Bactericidal activity at baseline						
Clinical question of interest: The interest lies in evaluate the bactericidal activity at baseline in the primed group* and in the naïve group† against each MenB indicator strain, regardless of ICEs occurrence. **Rationale:** As the interest is in evaluating the bactericidal activity at baseline in the primed group and in the naïve group in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used.						
Secondary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each MenB indicator strain at Visit 1(Day 1)	• Administration of a vaccination forbidden by the protocol. • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for immunogenicity endpoints, i.e., the value for each of the endpoints is used regardless of whether or not the intercurrent event occurs	• Number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each MenB indicator strain, at Visit 1 (Day 1). • Number and percentage of participants with hSBA titers ≥LLOQ against each MenB indicator strain, at Visit 1 (Day 1). • hSBA GMTs against each MenB indicator strain at Visit 1 (Day 1).

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Secondary Estimand: Safety						
Clinical question of interest: The interest is to evaluate the safety of rMenB+OMV NZ throughout the study period. **Rationale:** As the interest is in evaluating the safety of one dose of rMenB+OMV NZ, in a real world setting where participant may not adhere to all the protocol requirements, considering all participants that are exposed to the study vaccine, the treatment policy strategy is used.						
Secondary	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	• Occurrence of solicited administration site and systemic events within 7 days following the first vaccination at Day 1 (Visit 1). • Occurrence of any unsolicited AEs within 31 days (including the day of injection) following the first vaccination at Day 1 (Visit 1). • Occurrence of AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period (from Day 1 to Day 31).	• Administration of a vaccination forbidden by the protocol. • Administration of a medication forbidden by the protocol. • Errors in first/booster dose vaccine administration: ○ Vaccine temperature excursion ○ Expired vaccine ○ Lower volume of vaccine ○ Other errors lead to vaccine not administered according to the protocol	A treatment policy strategy will be used for safety endpoints, i.e., the value for each of the safety endpoints is used regardless of whether or not the intercurrent event occurs.	• Percentage of participants reporting solicited administration site and systemic events within 7 days following the vaccination at Visit 1 (Day 1). • Percentage of participants with any unsolicited AEs within 31 days (including the day of injection) following the vaccination at Visit 1 (Day 1). • Percentage of participants reporting AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period.

Abbreviations: AE: adverse event; AESI: adverse event of special interest; GMR: geometric mean ratio; GMT: geometric mean titer; hSBA: human serum bactericidal assay; ICE: intercurrent event; LOD: limit of detection; LLOQ: lower limit of quantification; MenB: meningococcal bacteria belonging to N. meningitis serogroup B; SAE: serious adverse event.

*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life.

†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

** Four-fold increase (seroconversion) defined as:

- Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2;
- Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥2.

Table 5 Study estimand - exploratory objective

Estimand	Attributes					
	Study intervention	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Summary measure
				Description	Handling strategy	
Exploratory Estimand: The humoral immune response against serotype A, C, W and Y after 1 dose of rMenB + OMV NZ in the primed group* and in the naïve group†						
Clinical question of interest: The interest lies in assess the immune response against serotype A, C, W and Y to 1 dose of rMenB + OMV NZ in the primed group* and in the naïve group†, regardless of ICEs occurrence. **Rationale:** As the interest is in evaluating the bactericidal activity at baseline and evaluating the immune response against serotype A, C, W and Y to one booster dose in the primed group and to the first dose in the naïve group, in a real-life scenario, considering that participant may not adhere to all the protocol requirements, the treatment policy strategy is used.						
Exploratory	1 dose of rMenB+OMV NZ	Healthy participants aged 10 to 20 years old, who were primed with rMenB + OMV NZ (in either 2+1 or a 3+1 schedule) or who were naïve (never received any group B meningococcal vaccine).	hSBA titers against each ACWY serogroup at Visit 1 (Day 1) and Visit 2 (Day 31)	• Blood draws occurring outside the protocol-defined visit window. • Errors in first/booster dose vaccine administration: ○ Vaccine temperature excursion ○ Expired vaccine ○ Lower volume of vaccine ○ Other errors lead to vaccine not administered according to the protocol • Administration of a vaccination forbidden by the protocol • Use of a medication forbidden by the protocol. • Occurrence of medical condition forbidden by the protocol.	A treatment policy strategy will be used for immunogenicity endpoints, i.e., the value for each of the endpoints is used regardless of whether or not the intercurrent event occurs.	• Number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each ACWY serogroup at Visit 1 (Day 1) and Visit 2 (Day 31). • Number and percentage of participants with hSBA titers ≥LLOQ against each ACWY serogroup at Visit 1 (Day 1) and Visit 2 (Day 31) • Percentage of participants with four-fold increase** in hSBA titers against each ACWY serogroup at Visit 2 (Day 31) relative to Visit 1 (Day 1). • hSBA GMTs and GMRs against each ACWY serogroup at Visit 2 (Day 31) relative to Visit 1 (Day 1).

Abbreviations: GMR: geometric mean ratio; GMT: geometric mean titer; hSBA: human serum bactericidal assay; ICE: intercurrent event; LOD: limit of detection; LLOQ: lower limit of quantification; MenB: meningococcal bacteria belonging to N. meningitis serogroup B.

*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in either 3+1 or 2+1 schedule as infants in studies V72_28, V72_P12E1 V72_P13E1 or as routine practice during the first 2 years of life.

† Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

** Four-fold increase (seroconversion) defined as:

- Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2;
- Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥ 2.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 3b, open-label, multi-center study to assess the immune response and safety of a single booster dose of rMenB+OMV NZ when administered to healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ in a 2+1 or 3+1 schedule during the first 2 years of life.

The study will include 2 groups (see Figure 1):

- Primed group (n=234): participants who were primed with rMenB+OMV NZ in 2+1 or 3+1 schedule during the first 2 years of life in studies V72_28, V72_P12E1, V72_P13E1 or in routine practice will receive 1 dose of rMenB+OMV NZ.
- Naïve group (n=78): participants who are group B-meningococcal-vaccine-naïve within the same age range as the primed group will be recruited and will receive 2 doses of rMenB+OMV NZ, 1 month apart (with 30 days of interval).

Participants will be monitored for safety throughout the study period.

Duration of the study: For each participant enrolled the duration will be approximately 1 month.

Primary completion date: Last subject last visit (LSLV)

End of Study (EoS): LSLV or date of the last testing/reading released of the Human Biological Samples related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

Data collection: Standardized electronic case report form (eCRF) will be used. Solicited (administration site and systemic) events will be collected using a participant electronic diary (eDiary).

Safety Monitoring: Safety follow-up will be done as summarized in the SOA (Section 1.3).

4.2. Scientific rationale for study design

The purpose of this study is to assess the safety and immunogenicity of a single booster dose of rMenB+OMV NZ vaccine in participants aged 10 to 20 years of age who were previously primed with rMenB+OMV NZ during infancy period.

Adolescence represents the third peak of incidence of IMD after infancy and children. In adolescents and young adults primed during infancy, the immune memory is expected to persist despite low antibody titers and a booster dose could trigger an amnestic response resulting in higher immune response than in vaccine-naïve adolescents [Rollier, 2022]. Thus, information on the immune response elicited by a booster dose administered to adolescents that received complete primary series of rMenB+OMV NZ vaccine during their infancy is of interest for Health Care Professionals (HCPs), because a large number of infants vaccinated in NIPs are approaching to the adolescent age whereas currently there are no studies which adequately provide such data.

The primary objective of the study is to assess the superiority of a single dose of rMenB+OMV NZ in the primed participants aged 10 to 20 years compared to the first dose of rMenB+OMV NZ in the naïve participants against each MenB indicator strains. To demonstrate the superiority, the ratio of GMTs and the corresponding exact 2-sided 95% CIs will be calculated against each MenB indicator strains between the primed and naive group at 1 month post booster or first dose (Visit 2, Month 1).

The study population will include individuals that participated in studies V72P12E1, V72P13E1 and V72_28, and participants that received rMenB+OMV NZ as an infant in routine practice. This is the most suitable pool of candidates for the present study, since it includes participants from both rMenB+OMV NZ vaccine's parent clinical trials and participants vaccinated with rMenB+OMV NZ during infancy as part of a NIP, who have reached 10-20 years. A group of vaccine-naïve adolescents in the same age range will be enrolled and vaccinated with two doses of rMenB+OMV NZ according with the age-specific EU Product Information approved schedule. This group will act as a comparator for superiority and will provide information on pre-vaccination bactericidal activity and post-first vaccination bactericidal activity.

4.2.1. Participant input into design

For this study, no participant input was taken during study design development.

4.3. Justification for dose

Study intervention is provided as a suspension for injection in a pre-filled syringe and will be administered at a dosage of 0.5 ml at each vaccine administration. rMenB+OMV NZ vaccine is licensed and the requisite dose is well established through clinical studies.

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 visit or the last scheduled procedure shown in the SoA.

The EoS is defined as the date of the last subject last visit or the last testing released of the Human Biological Samples related to primary and secondary endpoints. If EoS is not equal to LSLV, it must be achieved no later than 8 months after LSLV.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

For primed group only:

- Participated who were primed with rMenB + OMV NZ in only either 3+1 or 2+1 schedule during the first 2 years of life in studies in studies V72_28, V72_P12E1, P72_13E1, or in routine practice as confirmed by electronic or paper vaccination record. (INC#1)

OR

For naïve group only:

- Electronic or paper vaccination record confirmed participant who has never received any group B meningococcal vaccine and is recruited in the same country as primed participants. (INC#1)

For all participants:

- Participants and/or participants' parent(s)/ legally acceptable representative(s) (LAR[s]), who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., return for follow-up visits). (INC#2)
- Written or witnessed/thumb printed informed consent obtained from the participant / parent(s)/LAR(s) of the participant prior to performance of any study-specific procedure. (INC#3)
- Written informed assent obtained from the participant (if applicable) along with informed consent from the participant's parent(s)/LAR(s) prior to performing any study specific procedure. (INC#4)

Note: For age 10-16 years, parents or LAR to give consent along with participants, based on country regulations for participants and for >16/18 to 20 years, participants give consent independent of parents/LARs, or as per local country regulations.

- A male or female between, and including, 10 and 20 years of age at the time of the first study intervention administration. (INC#5)
- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, hysterectomy, bilateral ovariectomy. (INC#6)

- Female participants of childbearing potential may be enrolled in the study, if the participant: (INC#7)
  - has practiced adequate contraception for 1 month prior to study intervention administration, and
  - has a negative pregnancy test on the day of study intervention administration, and
  - has agreed to continue adequate contraception during the entire study treatment period.

5.2. Exclusion criteria

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
- Known exposure to an individual with laboratory confirmed *N. meningitidis* infection, within 60 days prior to enrollment. EXC#2
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention. EXC#3
- Medical conditions representing a contraindication to intramuscular vaccination and blood draws. EXC#4
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required). EXC#5
- 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#6

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention during the period beginning 30 days before the first dose of study intervention (Day -29 to Day 1), or their planned use during the study period. EXC#7
- Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or planned use of long-acting immune-modifying treatments at any time up to the end of the study. EXC#8
  - Within 90 days prior to study intervention administration: for corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants or ≥0.5 mg/kg/day with maximum of 20 mg/day for pediatric participants. Inhaled and topical steroids are allowed.

  - Within 90 days prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication.

- Administration of immunoglobulins and/or any blood products or plasma derivatives within 180 days prior to study intervention administration and/or planned use at any time up to the end of the study. EXC#9

For primed group only:

- Participants who received additional dose(s) of group B meningococcal vaccine other than 2+1 or 3+1 schedule prior to study intervention administration. EXC#10

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 intervention (drug/vaccine/invasive medical device). EXC#11

5.2.4. Other exclusion criteria

- Pregnant or lactating female participant. EXC#12
- Any study personnel or their immediate dependents, family, or household member. EXC#13
- Child in care. EXC#14

  Child in care is defined as 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.

5.3. Lifestyle considerations

There are no lifestyle restrictions required for this study.

5.4. Screen failures

A screen failure refers to a participant who does not meet the eligibility criteria (inclusion/exclusion) criteria during the screening and is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated standards of reporting trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened (if appropriate). Rescreened participants should be assigned a new participant identifier for every screening/rescreening event. Previously assigned participant identifier(s) are to be recorded in the participants' eCRF.

5.5. Criteria for temporarily delaying enrolment /administration of study intervention/blood sampling

Enrollment / study intervention administration/blood sampling may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of enrollment and/or study intervention administration.

Note: Fever is defined as body temperature ≥ 38.0°C (100.4°F). The preferred location for measuring temperature will be axillary. If any other route is used for measuring temperature, this needs to be recorded in the eCRF.

- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Receipt of other vaccines that are not mentioned in the local approved label as concomitant administration. Bexsero can only be given, if related acute symptoms have been resolved (refers to the vaccine that are not listed as concomitant administration).
- There is a clinical circumstance that warrants delay of blood collection for immunogenicity assessments in this study: participant has received a dose of systemic antibiotics less than 72 hours before the intended blood collection. In the event that a participant meets this criterion for delay of blood collection, blood collection may proceed once the window for delay has passed.

For the second dose in the naïve group:

- The administration of the second dose of rMenB + OMV NZ in the naïve group should follow the warnings and precautions in the local approved label.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Table 6 Study intervention(s) administered

Study intervention name:	Meningococcal group B Vaccine (rDNA, component, adsorbed)^
Study intervention formulation	rp287-953 (50 µg)[1]; rp961c (50 µg)[1]; rp936-741 (50 µg)[1]; OMV NZ98/254 (25 µg PorA P1.4)[1]; [1]adsorbed on $Al(OH)_3$ (0.5 mg Al^{3+}); Water for injections
Presentation	Suspension for injection
Type	Investigational Biologic
Use	IMP
Non-IMP	N/A
Authorized AxMP/ Unauthorized AxMP	N/A
Route of administration	IM injection
Administration site:	
• **Location**	Deltoid
• **Directionality**	Upper
• **Laterality***	Non-dominant
Number of doses to be administered:	1 dose in the Primed group or 2 doses in the Naïve group
Volume to be administered by dose:**	0.5 mL
Sourcing	Provided centrally by the sponsor
Packaging and labeling:	Refer to the pharmacy manual for more details
Manufacturer:	GSK

Abbreviations: AxMP = Auxiliary medicinal product; EU = European Union; GSK = GlaxoSmithKline Biologicals SA; IMP = Investigational medicinal product; PhP = Pharmaceutical product; PLM = Product lifecycle management; IM = Intramuscular.

^ Refers to study intervention rMenB+OMV NZ vaccine (Bexsero).

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

** Refer to the pharmacy manual for the volume.

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

Table 7 Study arm(s)

Arm title	Primed group	Naïve group
Arm type	experimental	comparator
Regimen number	1 dose at Visit 1	2 doses (1 dose at each visit)
Arm description	10 to 20 years old participants who were primed with rMenB+OMV NZ in 2+1 or 3+1 schedule during the first 2 years of life in studies V72_28, V72_P12E1, V72_P13E1 or in routine practice will receive at Day 1 1dose of rMenB+OMV NZ	10 to 20 years old participants who are group B-meningococcal-vaccine-naïve within the same age range as the primed group will be recruited and will receive 2 doses of rMenB+OMV NZ, 1 month apart (with 30 days of interval).

6.1.1. Medical devices

- The GSK-manufactured medical device (or devices manufactured for GSK by a third party) provided for use in this study is a pre-filled syringe.
- Instructions for medical device use are provided in the Pharmacy Manual.
- All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9 and Section 10.6) and appropriately managed by GSK.

6.2. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants assigned to the study intervention may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3. Assignment to study intervention

Type of study	Open-label using central randomization via RTMS
Study using RTMS	All participants will be centrally assigned to allocate study intervention number using an RTMS. Study intervention will be dispensed and administered at the study visits as summarized in the SoA.
Study using pre-coded randomization provided to site	Participants will be recruited in a 3:1 ratio in the Primed group and the Naïve group. Due to the reason that the participants recruited in each group are distinct group of population, a sequential list will be used in RTMS for intervention allocation at Visit 1 (Day 1) and Visit 2 (Day 31). Participants will be assigned with a unique number (sequential number) in ascending numerical order at each study site. The sequential number encodes the participant's assignment to one of the two arms of the study, according to the-sequential schedule generated prior to the study by the statistics department at GSK sponsor.

RTMS = Randomization and Trial Supply Management; SoA = Schedule of activities.

6.4. Blinding, masking

Type of study	Interventional, open-label study
Open-label, no blinding at site level	open-label study
Open-label using central randomization via [RTMS]	This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using RTMS. The site will contact the RTMS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the eCRF.
Blinding of laboratory testing	The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.

Abbreviations: CRF = Case report form; GSK = GlaxoSmithKline Biologicals SA; RTMS = Randomization and Trial Supply Management.

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.

6.5. Study intervention compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the study site will be recorded in the source documents.

A record of the quantity of rMenB+OMV NZ dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records.

6.6. Dose modification

Not applicable.

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

There is no plan to provide continued access to the study intervention following the end of the study.

6.8. Treatment of overdose

Any dose of study vaccine greater than the dose advised as per protocol is considered an overdose. Overdose itself is not to be reported as an AE, however, any AEs associated with the overdose are to be reported in the relevant AE/SAE sections of the eCRF.

6.9. Prior and concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The past vaccination history of each Meningococal B vaccines and MenACWY vaccines should also be collected and recored in the eCRF along with:

- Reason for use.
- Dates of administration.
- Dosage information.

The site-specific contact of GSK (or GSK-delegate) should be contacted if there are any questions regarding concomitant or prior therapy.

Any antipyretic administered in the period starting 6 hours before study intervention and ending 12 hours after study interventions need to be recorded on the eCRF. An antipyretic is considered prophylactic when given in the absence of fever, to prevent fever from occurring.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if possible, continue other study procedures (e.g., safety or immunogenicity), planned in the study protocol according to the visit schedule described in the SoA (Section 1.3). If the participant does not agree to continue in-person visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information (e.g., telephone contact, retrieval of vital status information through medical records). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

Reasons
AE
Lost to follow-up
Physician decision
Pregnancy
Protocol deviation
Site terminated by sponsor
Study terminated by sponsor
Sponsor terminated study intervention
Withdrawal by participant
Other
Death

AE = Adverse event.

7.1.1. Contraindications to subsequent study intervention(s) administration

Not applicable for the primed group.

For the naïve group, please refers to the local approved label for contraindications to the second dose.

7.2. Participant discontinuation/withdrawal from the clinical study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason) without any negative consequences.

Although a participant is not obliged to provide any reason, the investigator should consider discussing with the participant or the participant's LAR, if appropriate. This

discussion should focus on the reasons for withdrawal to determine if there are ways to address the concerns, so that the participant could reconsider their withdrawal without unduly interfering with the participant's right to refuse or withdraw participation at any time.

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

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 available for the study analyses. The participant may request the destruction of their samples where practical and possible in accordance with local regulations, and the investigator must document this in the site study records.

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

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 as defined in Section 10.3.5.5.

Withdrawals will not be replaced.

7.3. Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls/other contact methods, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status information of the participant within legal and ethical boundaries for all participants

randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status of the participant is determined as deceased, this will be documented along with other relevant study information. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants/participants' parent(s)/LAR(s) who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of "screen failure."
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 40 mL.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as month and year of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to determine, assess, and monitor the representativeness of the trial participants.

Month and year of birth is collected to stratify the population and determine the impact of the study intervention by age.

8.1.2. Medical /vaccination history

Obtain the participant's medical/vaccination history (only vaccines history specified in the protocol to be collected) by interviewing the participant/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. The collection of Meningococal B vaccines and MenACWY vaccines history can be found in Section 6.9.

8.2. Efficacy and/or immunogenicity assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA.

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.

If allowed by informed consent, the samples collected in this study may also be used for further research to better understand the study disease(s) under evaluation and/or further characterize the immune response to the study vaccine(s) and/or to further understand other diseases and/or inform the development of new products. In addition, the samples may be used to develop new research methods, assays, and tests. To this end, all participants in countries where this is allowed will also be asked to give consent to further research at the time they give consent to join the study. Biological samples may also be shared with a contracted partner 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.

8.2.1. Biological samples

An overall volume of 40 mL (i.e. 20 mL at each visit) will be collected. Refer to SoA (Section 1.3) for information on volumes collected for different assessments.

8.2.2. Laboratory assays

Immunogenicity of rMenB+OMV NZ will be evaluated with assays measuring the serum bactericidal activity against a standard panel consisting of 4 *N. meningitidis* serogroup B indicator strains N men B fHbp (M14459), N men B NadA (96217), N men B NHBA (M13520) and N men B PorA (NZ98/254) using an exogenous source of complement. An exploratory objective on the immunogenicity of rMenB+OMV NZ vaccine to serogroup A (3125), C (C11), W (M01-240070) and Y (860800) strains will also be assessed in this study by measuring the serum bactericidal activity. The strains selected to measure the bactericidal activity primarily directed against each of the 4 major bacterial antigens included in the rMenB+OMV NZ vaccine as well as the strains against serogroup A, C, W, Y are presented in the table below.

Table 8 Laboratory assays

Test classification	System	*N meningitidis strains*	Method	Laboratory	Unit
Humoral Immunity (bactericidal activity)	Serum	N men B fHbp (M14459)	hSBA	GSK or a laboratory designated by GSK	1/dilution[a]
		N men B NadA (96217)			
		N men B NHBA (M13520)			
		N men B PorA (NZ98/254)			
Humoral Immunity (bactericidal activity)*	Serum	N men A (3125)	hSBA	GSK or a laboratory designated by GSK	1/dilution[a]
		N men C (C11)			
		N men W (M01-240070)			
		N men Y (860800)			

fHbp : Factor H-binding protein; hSBA: human serum bactericidal assay; NadA: Neisseria adhesin A; NHBA : Neisserial heparin binding antigen; N men: Neisseria meningitidis; PorA: Porin protein A.

a. 1/dilution: reciprocal of the dilution giving 50% of killing

* Humoral immune response testing on serogroup A, C, W and Y strains belongs to the exploratory endpoints.

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

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.

8.2.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint		Group	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-Booster	Primed	234	N men B fHbp titer N men B NadA titer N men B NHBA titer N men B PorA titer N men A titer * N men C titer * N men W titer * N men Y titer *
	Pre-Dose 1	naïve	78	
Visit 2 (Day 31)	1 month Post-Booster	Primed	234	
	1 month Post-Dose 1 (Pre-Dose 2)	naïve	78	

* Exploratory endpoints.

8.2.4. Immunological correlates of protection

No generally accepted immunological CoP has been demonstrated so far for the antigen(s) used in the study intervention.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. History directed physical examination

- History directed physical examination will be performed for each participant.
- If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. See Section 5.5 for the list of criteria for temporary delay of study intervention administration. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.
- Physical examination at each study visit after the first study intervention administration will be performed only if the participant/participant's parent(s)/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

8.3.2. Vital signs

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

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

8.3.3. Pregnancy testing

- A urine pregnancy test must be performed for all female participants of childbearing potential before the administration of the first dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- See Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.4. Adverse events, serious adverse events, and other safety reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, events leading to discontinuation of study intervention (see Section 7.1), and other safety information and remain responsible for following up all AEs (see Section 7). This includes events reported by the participant (or when appropriate by parent(s)/LAR(s)).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 and/or Section 10.6.

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

All AEs/SAEs will be collected from the signing of the ICF until Visit 2 at the time points specified in the SoA.

This includes any AEs related to study participation (e.g., during screening, or related to study intervention, protocol-mandated procedures, invasive tests, or change to existing therapy) or related to a product defined in the study intervention(s) administered (Table 6).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

Table 10 Collection and reporting of safety information

Event	Pre-Dose*		D1		D7		D31** (Day of study conclusion)
Administration Site and systemic Solicited events†							
Unsolicited AEs							
AEs leading to withdrawal							
AESIs							
SAEs							
SAEs related to study participation or concurrent GSK medication/ vaccine							
Pregnancy#							

* i.e., consent obtained;
**Study conclusion happens on Day 31 (Visit 2) for the Primed group and the Naïve group
† Solicited AEs to be collected for 7 days following first vaccination, with ongoing solicited AEs collected until resolution or Day 31 (whichever occurs first).
# Pregnancy will be reported directly using the electronic Pregnancy Report form/ paper pregnancy report form as per standard GSK process when applicable.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 and/or Section 10.6. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

AE/SAE that occurs after the administration of the second dose of rMenB + OMV NZ in the naïve group will be classified as spontaneous adverse reaction reports. Healthcare professionals, study participants or LARs will be informed of the possibility to report these spontaneous adverse reactions to the GSK safety Department via the national spontaneous reporting system.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records per the local country requirements. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.7 for contact information.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant/participants' parent(s)/LAR(s) is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.5 and/or Section 10.6.4.4.

8.4.4. AESIs

Adverse events of special interest (AESI): Arthritis

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

Cases of arthritis are defined according to the following definition:

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

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

The list of preferred terms corresponding to the diagnosis of arthritis are those included in the Medical Dictionary for Regulatory Activities Standard MedDRA Query 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 electronic case report form page on arthritis to further characterize this AESI.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as AESI. Symptoms, signs, or conditions which might (or might not) lead to one of the above 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.

8.4.5. Regulatory reporting requirements for SAEs/AESIs

- Prompt notification by the investigator to the sponsor of an SAE/AESI is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting (including SUSAR reporting) to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.6.

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

Table 11 Timeframes for submitting safety events reports to sponsor/regulatory authorities

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	Electronic AEs report	24 hours*	Electronic AEs report
Pregnancies	24 hours*‡	Electronic pregnancy report	24 hours*	Electronic pregnancy report
AESIs	24 hours**‡	Electronic AEs report	24 hours*	Electronic AEs report
Fatal or life-threatening SUSAR	Within 7*** calendar days	NA		Sponsor to regulatory authorities
Non-fatal or non-life-threatening SUSARs	Within 15*** calendar days	NA		Sponsor to regulatory authorities

AE = Adverse event; AESIs = Adverse event of special interest; SAE = Serious adverse event.
* 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.
‡ If the electronic system is unavailable, the paper SAE data collection tool will be used to report the event within 24 hours. Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE/AESI, the investigator(s) must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.
*** 7/15 days or as per local country requirements.

8.4.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for postintervention contraception determined in Section 5.1, in line with applicable informed consent.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (see Section 10.3.5).
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. See Table 11 for reporting timeframes.

- Any poststudy pregnancy-related SAE in a pregnant person, and any SAE in a fetus or newborn as a consequence of exposure during pregnancy, if considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.
- Prior to continuation of study intervention following pregnancy in a study participant, the following must occur:
- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.4.7. Contact information for reporting SAEs, AESIs, pregnancies

Table 12 Contact information for reporting SAEs, AESIs, pregnancies

Study contact for questions regarding SAEs, AESIs, pregnancies and SAEs linked to device deficiencies Contact study team clinical lead or study assigned clinical research associate
Contacts for reporting SAEs, AESIs, pregnancies and SAEs linked to device deficiencies Available 24/24 hours and 7/7 days CCI [redacted]

Abbreviation: AESI = Adverse event of special interest; GSK = GlaxoSmithKline Biologicals SA; SAE = Serious adverse event.

8.4.8. Participant card

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

8.4.9. Medical device deficiencies

Devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a device deficiency can be found in Section 10.6.

Note: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

8.4.9.1. Time period for detecting medical device deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.9.2. Follow-up of medical device deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.9.3. Prompt reporting of device deficiencies to the sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor by email(refer to section 10.6.7 for detail).
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.9.4. Regulatory reporting requirements for device deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- 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.

8.5. Pharmacokinetics

Pharmacokinetics (PK) is not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamics (PD) is not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is described in Section 8.2.

8.10. Health economics or medical resource utilization and health economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to study start and it will include a more technical and detailed description of the statistical analyses introduced in this section. This section is a summary of the planned statistical analyses related to the primary and secondary endpoints.

9.1. Statistical hypothesis

The primary objective, as outlined in Section 3, is planned to be addressed using formal hypothesis testing.

The primary aim of the study is to demonstrate the superiority of the immune response to one booster dose of rMenB+OMV NZ in the primed group, compared to the first dose in the naïve group against each MenB indicator strain.

For the primary estimand, the following 1-sided hypotheses are planned to be tested simultaneously against each of the four MenB indicator strains, considering a 1-sided type-I error of 2.5%.

Let π_k be defined as the ratio between the GMT in the primed group and the GMT in the naïve group at 1 month following the booster or first dose for each of the strains, and k = 1,2,3,4 represents the specific indicator strain (M14459, 96217, NZ98/254, and M13520).

H_{0k}: $\pi_k \leq 1$ vs. H_{1k}: $\pi_k > 1$

The null hypothesis will be rejected (i.e., superiority demonstrated) if the lower limit of the two-sided 95% confidence interval (CI) of the ratio of the GMTs is greater than 1. The study will be claimed a success if each of the 4 single hypotheses is rejected simultaneously.

9.2. Analysis sets

Analysis sets are summarized in Table 13.

Table 13 Analysis Set

Analysis Set	Description
Enrolled	All participants who entered the study (who were assigned with the subject ID or received study vaccine or underwent a post screening study procedure). Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.
Exposed	All participants who entered the study and received at least 1 dose of study vaccine.
Persistence Analysis Set	All participants who entered the study and have immunogenicity data at baseline.
Full Analysis Set (FAS)	All participants who received at least 1 dose of study vaccine and have post-vaccination immunogenicity data.
Supportive Immunogenicity Analysis Set	All participants who received at least 1 dose of study vaccine who comply with the procedures and intervals defined in the protocol, who did not present with a medical condition leading to exclusion, have the blood collection within an appropriate window; have available data concerning immunogenicity endpoint measures and have no other major protocol deviations.

9.3. Statistical analyses

The immunogenicity primary and secondary objectives and the exploratory analysis will be conducted on the Full Analysis Set. The persistence secondary objectives will be conducted on the Persistence Analysis Set and the safety analysis will be based on the Exposed Set. The supportive analysis will be conducted on the Supportive Immunogenicity Analysis Set.

9.3.1. Primary endpoint analyses

9.3.1.1. Definition of endpoint(s)

For the definition of the primary endpoint, please refer to Table 3.

9.3.1.2. Main analytical approach

Objective	Analysis
To demonstrate the superiority of the immune response to one booster dose of rMenB + OMV NZ in the primed group*, compared to the first dose in the naïve group† against each MenB indicator strain.	**Analysis set:** Full Analysis Set **Statistical Methods:** The hSBA titers at 1 month after the first or booster dose (Visit 2, Day 31) will be logarithmically transformed (base10) to fulfill the normal distribution assumption. For each MenB indicator strain the GMTs for the primed* and the naïve† group will be obtained from an ANOVA and then exponentiating the log-transformed means and their 95% CIs. The ratio of the GMTs between the primed* and naïve† group and the corresponding 95% CIs will be calculated exponentiating the difference of the log-transformed means and the lower and upper limits of the 95% CIs on the difference obtained from the ANOVA model above. The null hypothesis will be rejected if the lower limit of the 95% confidence interval of the ratio of the GMTs is >1.

CI: confidence interval; LL: lower limit; MenB: meningococcal bacteria belonging to serogroup B.
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

9.3.1.3. Subgroup analysis

Subgroup analysis for the primary objective based on the age will be performed.

9.3.1.4. Supportive analysis

Objective	Analysis
To demonstrate the superiority of the immune response to one booster dose of rMenB + OMV NZ in the primed group*, compared to the first dose in the naïve group† against each MenB indicator strain.	**Analysis set:** Supportive Immunogenicity Set **Statistical Methods:** The hSBA titers at 1 month after the first or booster dose (Visit 2, Day 31) will be logarithmically transformed (base10) to fulfill the normal distribution assumption. For each MenB indicator strain the GMTs for the primed* and the naïve† group will be obtained from an ANOVA and then exponentiating the log-transformed means and their 95% CIs. The ratio of the GMTs between the primed* and naïve† group and the corresponding 95% CIs will be calculated exponentiating the difference of the log-transformed means and the lower and upper limits of the 95% CIs on the difference obtained from the ANOVA model above.

CI: confidence interval; MenB: meningococcal bacteria belonging to serogroup B.
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

9.3.1.5. Sensitivity analysis

Objective	Analysis
To demonstrate the superiority of the immune response to one booster dose of rMenB + OMV NZ in the primed group*, compared to the first dose in the naïve group† against each MenB indicator strain.	**Analysis set:** Full Analysis Set **Statistical Methods:** As a sensitivity analysis, an Augmented Inverse Probability Weighting (AIPW) estimator will be used. The latter differs from a standard IPW in that it incorporates regression models for the endpoint variable to improve efficiency and consistency of the estimator [Mao, 2019]. Before performing the analysis, the endpoint variable, i.e., the hSBA titers at 1 month after the first or booster dose (Visit 2, Day 31), will be logarithmically transformed (base10). For each MenB indicator strain, the GMTs for the study groups (primed* and naïve†) will be computed.

CI: confidence interval; LL: lower limit; MenB: meningococcal bacteria belonging to serogroup B.
*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.
†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

9.3.2. Secondary endpoints analyses

Objective	Analysis
To evaluate the humoral immune response to one booster dose of rMenB+OMV NZ in the primed group*, compared to the first dose in naïve group† against each MenB indicator strain.	**Analysis set:** Full Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) against each MenB indicator strains and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be determined at 1 month after booster or first dose (Visit 2, Day 31). Between group difference (primed group vs naïve group) at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥LLOQ against each MenB indicator strain and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be determined at 1 month after booster or first dose (Visit 2, Day 31). Between group difference (primed group vs naïve group) at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The number and percentage of participants with four-fold increase** in hSBA titers at 1 month after booster or first dose (Visit 2, Day 31) relative to baseline (Visit 1, Day 1) and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated against each MenB indicator strain. Between group difference (primed group vs naïve group) at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.
	Analysis set: Full Analysis Set **Statistical Methods**: The hSBA GMTs and GMRs at 1 month after booster or first dose (Visit 2, Day 31) compared to Visit 1 (Day 1) will be calculated against each MenB indicator strain. GMRs ratio between the primed group the naïve group at one month after the booster or first dose will be calculated, as well as their associated 95% CIs.

Objective	Analysis
To evaluate the bactericidal activity at baseline in the primed group* and in the naïve group†.	**Analysis set:** Persistence Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥4 (or ≥LOD if LOD >4) and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated against each MenB indicator strain at baseline (Visit 1, Day 1). Between group difference (primed group vs naïve group) at baseline will be calculated, as well as their associated 95% CIs.
	Analysis set: Persistence Analysis Set **Statistical Methods**: The number and percentage of participants with hSBA titers ≥LLOQ and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated against each MenB indicator strain at baseline (Visit 1, Day 1). Between group difference (primed group vs naïve group) at baseline will be calculated, as well as their associated 95% CIs.
	Analysis set: Persistence Analysis Set **Statistical Methods**: The hSBA GMTs will be calculated against each MenB indicator strain at Visit 1 (Day 1). GMTs ratio between the primed group the naïve group at baseline will be calculated, as well as their associated 95% CIs.
To evaluate the safety of rMenB+OMV NZ throughout the study period.	**Analysis set:** Exposed **Statistical Methods**: The number and percentage of participants reporting solicited administration site and systemic events within 7 days (including the day of injection) following booster or first vaccination at Visit1, (Day 1) will be presented. All solicited events will be summarized according to defined severity grading scales. Number and percentages of participants experiencing each event will be presented for each symptom severity. Post-vaccination solicited events reported from Day 1 to Day 7 will be summarized by maximal severity and by vaccine group, excluding the 30-minutes measurement, which will be summarized separately. The severity of solicited administration site events will be summarized. Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of participants reporting use.
	Analysis set: Exposed **Statistical Methods**: The number and percentage of participants with any unsolicited AEs within 31 days (including the day of injection) following the first vaccination at Visit 1 (Day 1) will be presented. The number and percentage of participants reporting AESI (arthritis), SAEs, AEs leading to withdrawal throughout the study period will be presented. This analysis applies to all AEs occurring during the study, judged either as related or not related to vaccination by the investigator, recorded in AE eCRF, with a start date on or after the date of first vaccination. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. All AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class and preferred term within system organ class. These summaries will be presented by vaccine group and by interval of study observation. When an AE occurs more than once for a participant, the maximal severity and strongest relationship to the vaccine group will be counted. Data listings of all AEs will be provided by participant. In addition, AEs in the categories above will be provided as listed data.

AE: adverse event; AESI: adverse event of special interest; CI: confidence interval; GMT: geometric mean titer; GMR: geometric mean ratio; LOD: limit of detection; LLOQ: lower limit of quantification; MenB: meningococcal bacteria belonging to serogroup B; SAE: serious adverse event;

*Primed group: healthy participants aged 10 to 20 years old, who were primed with rMenB+OMV NZ as infants in studies V72_28, V72_P12E1 or V72_P13E1 or as routine practice.

†Naïve group: healthy participants aged 10 to 20 years old, who never received any group B meningococcal vaccine and who will be recruited in the same country as primed participants.

** Four-fold increase (seroconversion) defined as:

- Post-vaccination hSBA titers ≥ 8 for subjects with pre-vaccination hSBA titers < 2;
- Post-vaccination hSBA titers ≥ 4 times the pre-vaccination hSBA titers for subjects with pre-vaccination hSBA titer ≥2.

9.3.3. Exploratory endpoint analyses

The analyses of the exploratory endpoint will be conducted on the Full Analysis Set and will be described in the Statistical Analysis Plan (SAP).

9.4. Interim analyses

Not applicable.

9.5. Sample size determination

To demonstrate the superiority of the humoral immune response to one booster dose of rMenB+OMV NZ vaccine administered to participants aged 10 to 20 years that were primed in their early life, compared to the first dose in naïve group, the following hypothesis will be tested simultaneously against each of the four MenB indicator strains:

Null hypothesis vs. alternative hypothesis:

$$H_{0k}: \pi_k \leq 1 \text{ vs. } H_{1k}: \pi_k > 1,$$

where k = 1,2,3,4 corresponds to the 4 indicator strains (M14459, 96217, NZ98/254, and M13520) and π_k represents the ratio between the GMT in the primed group and the GMT in the naïve group at 1 month following the booster or first dose for each of the strains.

The null hypothesis will be rejected (i.e., superiority demonstrated) if the lower limit of the two-sided 95% confidence interval (CI) of the ratio of the GMTs is greater than 1. The study will be claimed a success if each of the 4 single hypotheses are rejected simultaneously.

Table 14 shows the power to demonstrate the superiority of the humoral immune response to an additional booster dose of rMenB+OMV NZ vaccine compared to the first dose in naïve group. i.e., the lower limit of the two-sided 95% CI of the ratio of the GMTs at 1 month after the booster or first dose of the rMenB+OMV NZ vaccine is greater than 1. Assumptions on the actual ratio were taken from V72_75 trial [Santolaya, 2012] considering participants from group 3b (V72P10), as the trial designs and age groups considered are the one closest to the current study. It is assumed that the participants in the current study will have antibody responses similar to those observed in those previous study.

With a sample size of 280 evaluable participants using a two sample T-test assuming equal variance, given a one-sided type I error level of 2.5% for each test, the probability to reject the null hypothesis when it is false (power) is 91.3%, 99.9%, 100% respectively for strains M13520 (NHBA), NZ98/254 (PorA) and both M14459(fHbp) and 96217 (NadA) strains. The overall power is 91.2%, the product of the 4 individual strain powers. With an assumed 10% of non-evaluable participants a and a 3:1 participant ratio between group, the number of participants to be enrolled will be 312, 234 in the primed group and 78 in the naïve group.

The purpose of this study is to establish the immunogenicity and safety of a single booster dose in adolescents, as such a sufficient enrolment is needed in the primed group for this purpose. Participants in the control group are enrolled to provide immunogenicity and safety for comparison, while the safety, tolerability and immunogenicity of a 2-dose schedule of Bexsero in adolescents and young adults is well-established. Furthermore, considering that the study will also be conducted in countries where Bexsero is part of the infant NIP, there could be difficulty in finding naïve subjects, and a 3:1 ratio will improve the study feasibility.

Table 14 CCI
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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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
  - Applicable International Council on Harmonisation (ICH) Good clinical practices (GCP) guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, Informed assent form (IAF), ICF, IB, and other relevant documents must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs 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 course of the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants/participants' parent(s)/LAR(s) and answer all questions regarding the study.
- Potential participants/participants' parent(s)/LAR(s) must be informed that their participation is voluntary. They or their parents/LAR(s) will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection, where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant/participant's parent(s)/LAR(s).
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the end of the study is reached. 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. Please refer to the local regulation for the duration of mandatory retention period for samples.
- The medical record must include a statement that physical informed consent was obtained before the participant was enrolled in the study and the date the physical consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical copy of the ICF(s) must be provided to the participant or their parents/LAR.
- The investigator must obtain assent from the minor participant in addition to the consent provided by the participants' parent(s)/LAR(s) when a minor can assent to participate in a study. The investigator is also accountable for determining a minor's capacity to assent to participation in a research study according to the local laws and regulations.
- In accordance with local laws and regulations, participants who become legally emancipated during the study, i.e., reach the legal age of consent, must be reconsented.

- The participant must provide consent by signing an ICF, which summarizes the study, includes a consent statement and provides documentation that the participant agrees to continue participating in the study.
- If the participant has incapacitation/physical and/or cognitive disabilities and cannot provide consent, the parent(s)/LAR(s) can provide consent by signing the ICF on their behalf.
- The investigator needs to explain to the parent(s)/LAR(s) of the participant with incapacitation/physical and/or cognitive disabilities of the potential benefits directly linked to the medical condition that the participant suffers and if this benefit outweighs the risk involved with participating in the trial.

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

The ICF will contain a separate section that addresses the use of remaining samples for optional further research related and not related to this study. The investigator or authorized designee will explain to each participant the objectives of the further research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

In case of unexpected pregnancy, participant must be informed that personal information (PI) such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

If a participant becomes pregnant during the study, the investigator or authorized designee will explain the benefits and risks of continuing or stopping the study intervention to the participant to allow an informed decision based on available data. Pregnant participants who choose to continue should complete an additional ICF specific to the benefit-risk consideration of study intervention exposure during pregnancy.

10.1.4. Recruitment strategy

Since this is a booster study, the target population is already known. A third-party vendor, and the sponsor will develop posters and flyer pads, a dear patient letter and that may be used in local outreach efforts. These items will provide basic information and site contact information and are designed to assist with recruitment.

Recruitment will be monitored throughout the study and mitigation plans put in place if needed.

10.1.5. Data protection

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

- 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.
- The participant/participants' parent(s)/LAR(s) must be informed that their personal/their child's study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant/participants' parent(s)/LAR(s), that their/their child's data will be used as described in the informed consent.
- The participant/participants' parent(s)/LAR(s) must be informed that their/their child's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- 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.

10.1.6. 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. In addition, where regulations require submission of other intermediate data analysis(es)/interim analysis(es), these results will be disclosed along with the final results summary.
- 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 all 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. Where required by applicable regulatory requirements, the layperson summary of results

will also be posted on health authority registers/public registers. The full study report will be made available upon request or within the required timelines by local regulation, 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 randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-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.

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

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

Abbreviations: CTA = Clinical trials application; EU = European Union
* As defined in the study protocol.

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

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

10.1.7. Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be predefined in the Study Management Plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the Clinical study report (CSR).
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor will report any serious breaches of this protocol, ICH GCP guidelines or local regulations to the regulatory authorities to comply with regulatory requirements.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- 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

- For this study there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF/eDiaries or entered in the eCRF/eDiaries that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in e.g., source data acknowledgment or monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as first subject first visit (FSFV) (first ICF signature date) at a country-level.

Study/Site termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

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

10.1.10. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

The tests detailed in Table 8 will be performed at GSK or GSK designated lab(s).

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

A urine pregnancy test will be conducted as needed for women of childbearing potential (refer to Section 8.3.3).

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

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

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

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (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 diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death.
b. Is life threatening. 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization. • In general, hospitalization 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 hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity. • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
f. Other situations: • Possible Hy's Law case: ALT ≥3x Upper limit of normal (ULN) AND total bilirubin ≥2x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or International normalized ratio (INR) >1.5 must be reported as SAE. • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

– Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, or convulsions.

10.3.3. Solicited events

- Definition of solicited event

- Solicited events are predefined administration site events and systemic events for which the participant/participant's parent(s)/LAR(s) are specifically questioned, and which are noted by the participant/participant's parent(s)/LAR(s) in their eDiary.
- Solicited Adverse Events are AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period

a Solicited administration site events

The following administration site events will be solicited:

Table 15 Solicited administration site events

Pain at administration site
Redness at administration site
Swelling at administration site
Induration at administration site

b Solicited systemic events

The following systemic events will be solicited:

Table 16 Solicited systemic events.

Fever (body temperature ≥ 38.0°C/100.4°F)
Headache
Myalgia (muscle pain)
Arthralgia (joint pain)
Fatigue (tiredness)
Nausea

Fever is defined as body temperature ≥ 38.0°C (100.4°F). The preferred location for measuring temperature in this study will be axillary.

Note: Participants/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/participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the eDiary.

10.3.4. Unsolicited AE

- Definition of unsolicited AE

- An unsolicited AE is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have

been communicated by participants/participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs.

- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants/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/participant's parent(s)/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 nor perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

10.3.5. Recording, assessment, and follow-up of AEs, SAEs, AESIs, and pregnancies

10.3.5.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant identifier, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned competent authority (CA) via the national spontaneous reporting system. These will be classified as spontaneous Individual case safety reports (ICSRs).

An eDiary will be used in this study to capture solicited administration site or systemic events. Anyone who measures administration site or systemic events and will record the event in the eDiary should be trained on using the eDiary, including the participant/participant's parent(s)/LAR(s). This training must be documented in the participant's source record.

For each solicited and unsolicited AE the participant experiences, the participant/participant's parent(s)/LAR(s) will be asked if they/their child received medical attention (i.e., MAAE which is defined as unscheduled visit to or from healthcare professional for any reason, including emergency room visits). This information will be recorded in the participant's eDiary and in the participant's eCRF as part of normal AE reporting (unsolicited AEs) as applicable. Medical attention received for SAEs/AESIs will have to be reported using the normal AE reporting process in the eCRF.

If any individual other than the participant/participant's parent(s)/LAR(s) is making entries in the eDiary, their identity must be documented in the participant's source record.

All solicited events that occur during 7 days following administration of the dose 1 of study intervention (Day 1 to Day 7) must be recorded into the eDiary, irrespective of intensity. Ongoing solicited AEs after 7 days should continue to be collected until resolution or Day 31 (whichever occurs first). An automatic reminder to complete the eDiary will be sent to the participants during this time frame. Daily eDiary compliance will be checked by the investigator or delegate on the eDiary portal. In case of non-compliance, the investigator should contact the participant to remind the importance of daily entries. The investigators will have to review the eDiary data real-time and contact the participant, participant's parent(s)/LAR(s) for additional information, if necessary, no later than 36 hours after the solicited event(s) was/were submitted through the eDiary. If the collection of solicited AEs was not possible for any reasons via the eDiary and participants reported solicited AEs to the investigator, then site staff should encode this information as detailed below for errors or missed reporting.

After review and verbal discussion of the eDiary entries with the participant, participant's parent(s)/LAR(s), if there are eDiary errors or missed reporting, the following actions should be taken: eCRF can be used for eDiary errors or missed reporting. If any data updates on participant reported data are requested by the participant or Investigator , those requests should be raised and recorded in the eCRF by the site as soon as possible (e.g. within 36h after midnight of each solicited event reporting day) to avoid potential recall bias.

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.

Note: eDiary may be completed in by a minor participant as of and including 10 years of age under the supervision of the participant's parent(s)/LAR(s) provided the minor is capable of assessing and reporting the information to be recorded on eDiary. The ultimate accountability for completion of the eDiary remains with the participant's parent(s)/LAR(s). The investigator should discuss this accountability with the participant's parent(s)/LAR(s).

The investigator or delegate should verify the reported information during a discussion with the minor participant preferably in the presence of their parent(s)/LAR(s).

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, AESI, SAE reported during the study and assign it to one of the following categories:

- Mild (Grade 1):
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate (Grade 2):
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3):
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Table 17 Intensity scales for solicited events in participants of 6 years of age or more

Event	Intensity grade	Parameter
Pain at administration site	0	None.
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at administration site	0	<25 mm
	1	25 to 50 mm
	2	51 to 100 mm
	3	>100 mm
Swelling at administration site	0	<25 mm
	1	25 to 50 mm
	2	51 to 100 mm
	3	>100 mm
Administration site induration	0	<25 mm
	1	25 to 50 mm
	2	51 to 100 mm
	3	>100 mm
Fever*	0	<38.0°C (<100.4°F)
	1	38.0°C (100.4°F) to 38.4°C (101.1°F)
	2	38.5°C (101.2°F) to 38.9°C (102.0°F)
	3	>38.9°C (>102.0°F)
Headache	0	None
	1	Mild: Symptom is easily tolerated.
	2	Moderate: Interferes with normal activity.
	3	Severe: Prevents normal activity.
Myalgia (muscle pain)	0	None
	1	Mild: Symptom is present but does not interfere with activity.

Event	Intensity grade	Parameter
	2	Moderate: Interferes with normal activity.
	3	Severe: Prevents normal activity.
Arthralgia (joint pain)	0	None.
	1	Mild: Symptom is present but does not interfere with activity.
	2	Moderate: Interferes with normal activity.
	3	Severe: prevents normal activity.
Fatigue (tiredness)	0	None
	1	Mild: Symptom is easily tolerated.
	2	Moderate: Interferes with normal activity.
	3	Severe: Prevents normal activity.
Nausea	0	None
	1	Mild: Symptom is easily tolerated
	2	Moderate: Interferes with normal activity.
	3	Severe: Prevents normal activity.

* Refer to the SoA for the preferred location for temperature measurement.

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality using GSK's 2-point scale (i.e., either related or unrelated) for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

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

10.3.5.5. Follow-up of AEs, SAEs, AESIs and pregnancies

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE/AESI/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESI (as defined in the Section 8.4.4) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Follow-up during the study

AEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

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

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using electronic pregnancy report and the AE

Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery, unless the local laws and regulation require a longer follow-up period.

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

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.5.7.

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

When additional SAE, AESI or pregnancy information is received after 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 sent to the study contact for reporting SAEs (see Section 8.4.3).

10.3.5.7. Reporting of SAEs, AESIs, and pregnancies

SAE reporting to GSK/GSK designee via an electronic data collection tool:

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the site-specific contact of GSK (or GSK-delegate) by telephone.
- Contacts for SAE reporting can be found in Section 8.4.7.

SAE reporting to GSK/GSK designee via paper data collection tool:

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the site-specific contact of GSK (or GSK-delegate).
- In rare circumstances and in the absence of email, notification with a copy of the SAE data collection tool sent by facsimile transmission is acceptable.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. WOCBP

Women in the following categories are considered Woman of childbearing potential (WOCBP) (fertile):

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. WONCBP

Women in the following categories are considered Woman of non-childbearing potential (WONCBP):

- Premenarchal: Tanner stage 1 (prepubertal).
- Permanently sterile due to one of the following procedures:

a. Documented hysterectomy.

b. Documented bilateral salpingectomy.

c. Documented bilateral oophorectomy.

For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

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

- **Postmenopausal female.**

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high Follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or Hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 18).

Table 18 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation. – Oral. – Intravaginal. – Transdermal.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. – Injectable. – Oral (if allowed by local regulation or if it is part of standard medical practice in the country).
Highly effective methods that are user independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
• IUD.
• IUS.
• Bilateral tubal occlusion/ligation.
• Vasectomized partner. – A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Male partner sterilization prior to the female participant's entry into the clinical study, and this male is the sole partner for that participant. – The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner.
• Sexual abstinence. – Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

IUD = Intrauterine device; IUS = Intrauterine hormone-releasing system; WOCBP = Woman of non-childbearing potential.

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

10.5. Appendix 5: Liver safety requirements and guidelines

Not applicable.

10.6. Appendix 6: Medical device AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to medical devices/device components of combination products provided for use in the study by the sponsor. See Section 6.1.1 for the list of medical devices/device components of combination products.

10.6.1. Definition of medical device AE and ADE

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

10.6.2. Definition of medical device SAE, SADE, and USADE

A medical device SAE is any serious AEs that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
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 Serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the IB (see Section 2.3).

10.6.3. Definition of device deficiency

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

10.6.4. Recording and follow-up of medical device AEs and/or SAEs and device deficiencies

10.6.4.1. Medical device AE, SAE, and device deficiency recording

- When a medical device AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant medical device AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the medical device AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.6.4.2. Assessment of intensity

See Section 10.3.5.2.

10.6.4.3. Assessment of causality

See Section 10.3.5.3.

10.6.4.4. Follow-up of medical device AE/SAE and device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.6.5. Reporting of medical device SAEs

Medical Device SAE Reporting to GSK/GSK designee via an Electronic Data Collection Tool:

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the site-specific contact of GSK (or GSK-delegate) by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK device they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.7.

Medical device SAE reporting to GSK/GSK designee via paper data collection tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the site-specific contact of GSK (or GSK-delegate).
- In rare circumstances and in the absence of email, notification with a copy of the SAE paper data collection tool sent by facsimile transmission is acceptable.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.6.6. Reporting of SADEs

SADE Reporting to GSK

Note: There are additional reporting obligations for device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.6.7. Reporting of device deficiencies

- Reporting to GSK

If a study participant and/or an Associated Person (e.g., spouse, caregiver, site staff) experiences a device deficiency, the device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization letter to contact physician.

If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed, to obtain consent.

- All device deficiencies that are not related to an AE or SAE should be reported via email to CCI [redacted], using the device deficiency report form.
- If the device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to CCI [redacted] only.
- If the device incident is linked to an SAE, please email the medical device deficiency report form to CCI [redacted] and CCI [redacted] within 24 hours. See Section 8.4.7 for reporting.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.7. Appendix 7: Country-specific requirements

The study is conducted in compliance with CTR 536/2014 regulation.

The sponsor will provide written summaries of the status of the study, information on SAEs or other significant safety findings to the IEC/IRB in accordance with local regulatory requirements.

The sponsor will report SUSAR to the Eudravigilance database to comply with regulatory requirements.

10.8. Appendix 8: Protocol amendment history

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

Amendment EU-1 (16 Jul 2025)

Overall rationale for the Amendment: Amendment EU-1 is an amendment in response to EU CTR feedback to specify the procedure for reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database.

Summary of changes table of previous amendment:

Section # and title	Description of change	Brief rationale
LIST OF ABBREVIATIONS AND DEFINITIONS	Added EU CTR – European Union Clinical Trials Regulation	To introduce and define all abbreviations.
5.1 Inclusion Criteria Inclusion Criterion 4	The note was updated with 'or as per local country regulations' for clarification.	To comply with EU CTR requirements.
8.4.5 Regulatory reporting requirements for SAEs/AESIs	The section was updated to include information about Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting.	To comply with EU CTR requirements.
10.7 Appendix 7 Country-specific requirements	The Section was added to align protocol with EU CTR.	To comply with EU CTR requirements.

10.9. Appendix 9: Protocol deviations

Protocol deviations are not allowed. The plans for detecting, review and reporting of protocol deviations is described in protocol deviation management plan.

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