Protocol Amendment 4

Study ID: 212458

Official Title of Study: A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II)

NCTID: NCT04886154

Date of Document: 11 APR 2022

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

Primary study intervention and number	GlaxoSmithKline Biologicals SA (GSK)'s combined meningococcal groups A, B, C, W and Y vaccine (GSK4023393A)
Other study intervention(s)	**Phase I** • Placebo **Phase II** • GSK's meningococcal group B vaccine (*Bexsero*) • GSK's combined meningococcal groups A, C, Y and W-135 conjugate vaccine (*Menveo*) • Placebo
eTrack study number and abbreviated title	212458 (MENACWY=CCI 001 PRI)
EudraCT number	2020-004741-37
Date of protocol	Final: 11 January 2021
Date of protocol amendment	Amendment 1 Final: 7 May 2021 Amendment 2 Final: 21 June 2021 Amendment 3 Final: 29 September 2021 Amendment 4 Final: 22 March 2022
Title	A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II).
Brief title	A study on the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine in healthy adolescents and adults.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.1

Protocol Amendment 4 Sponsor Signatory Approval

eTrack study number and abbreviated title	212458 (MENACWY=[redacted]001 PRI)
EudraCT number	2020-004741-37
Date of protocol amendment	Amendment 4 Final: 22 March 2022
Title	A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II).
Sponsor signatory	Daniela Toneatto, Clinical and Epidemiology Project Lead
Signature	_____
Date	_____

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

Protocol Amendment 4 Investigator Agreement

I agree:

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

Hence, I:

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

eTrack study number and abbreviated title	212458 (MENACWY=CCI -001 PRI)
EudraCT number	2020-004741-37
Date of protocol amendment	Amendment 4 Final: 22 March 2022
Title	A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II).
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Sponsor study contact for reporting of a Serious Adverse Events (SAEs)

GSK central back up study contact for reporting SAEs: refer to the protocol Section 8.3.3.1.

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

5. GSK Helpdesk for emergency unblinding

Refer to the protocol section 6.3.5.4.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 4 (22 March 2022)

Overall rationale for the current Amendment: This protocol has been amended to add 2 dosing schedules in the Phase II Sourcing part to support the finalization of assay development, further clinical testing, as well as assay stability monitoring and maintenance.

Additional changes have been made to update the sample size, planned schedule of analyses and/or to improve the clarity of the text. Refer to Section 10.10.1 for details.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 1.3 Schedule of activities, Table 5, Table 6, Table 7, Table 8, Table 9 and Table10 Section 3 Objectives and endpoints, Table 11 Section 4.1.2.2. (Study design) Phase II Sourcing Section 4.2 Scientific rationale for study design Section 6.1 Study intervention(s) administered Section 6.6 Continued access to study intervention after the end of the study Section 6.8 Concomitant therapy Section 8 Study assessments and procedures; Study procedures in special circumstances. Section 8.1.1.1 Blood sample Section 8.1.3 Immunological read-outs Section 8.3.1 Time period and frequency for collecting AE, SAE and other safety information Section 9.2.3: (Sample size determination) Phase II Sourcing	Two (2) dosing schedules have been added in the Phase II Sourcing part.	The wider dosing schedules have been included to support the finalization of assay development, further clinical testing, as well as assay stability monitoring and maintenance.

Section # and title	Description of change	Brief rationale
Section 9.4.3 Primary endpoint(s) – Phase II (Sourcing) Section 9.4.6 Tertiary endpoint(s) – Phase II (Sourcing) Section 10.1.9.1 Study conclusions Section 10.3.8 Recording and follow-up of AEs, SAEs, AESIs and pregnancies Section 10.3.9.3 Medically attended visits		
Section 4.4 End of study definition	Added a sentence to the definition for clarification.	To explain that in case the date of last testing occurs prior to LSLV, the LSLV will be the EoS.
Section 5.5 Criteria for temporarily delaying enrolment/ randomisation/ study intervention administration/blood sampling Section 10.3.9.5 Recording of AEs related to COVID-19	Update has been done to the COVID-19 related wording in these sections.	To align to the current COVID-19 guidelines as per WHO and/or local regulations.
Section 6.3.5 Blinding and unblinding	Added wording to make clear that unblinding will be done phase wise.	To clarify that the study will be unblinded after the completion of each Phase rather than at the end of the entire study.
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Section 9.5. Interim analyses	The sequence of analyses and statistical considerations for interim analysis have been updated.	The sequence of analyses has been presented in detail.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale: *Neisseria meningitidis* infections causing invasive meningococcal disease (IMD) are an important public health concern worldwide due to the substantial morbidity and mortality they cause, as well as the transmissibility of these infections. Ninety percent of meningococcal meningitis and septicaemia are caused by only 5 *N. meningitidis* serogroups: A, B, C, W and Y.

GSK is currently developing a MenABCWY combination vaccine intended to protect against IMD caused by all 5 meningococcal serogroups. C
C

The early clinical development plan consists of a seamless Phase I/II study. The first-time-in-human (FTIH), Phase I part of this study will be conducted in healthy adults in a dose-escalating fashion with 2 formulations of the investigational CCI and will serve as a safety lead-in to the Phase II study.

The Phase II part of the study will be conducted in 2 parts: The 'formulation and schedule-finding' part will follow in healthy adolescents and young adults and it is designed to select the vaccine formulation and the schedule to be tested in Phase III. The 'blood sourcing' part will be conducted in healthy adults in order to collect sufficient serum samples for the development of assays to be used in the CCI vaccine clinical development program. Phase II will assess the safety, the effectiveness and the immunogenicity of the above 2 formulations of the investigational CCI vaccine. *Bexsero* (rMenB+OMV NZ, hereafter referred to as MenB) and *Menveo* (hereafter referred to as MenACWY) will be administered as control vaccines for assessing the response to serogroups B and ACWY, respectively.

Objectives and endpoints: Refer to Table 11 for the study objectives and endpoints.

1.2. Schema

Refer to Figure 1, Figure 2 and Figure 3 in Section 4.1, Overall design.

1.3. Schedule of Activities (SoA)

(Amended 22 March 2022)

Table 1 Schedule of Activities – Phase I

Type of contact	Visit	Visit	Visit	PC	Visit	PC	PC	Notes
Visit/Phone call no.	V1	V2	V3	T1	V4	T2	T3	
Timepoint(s) [refer to Table 2 for visit windows]	Day 1	Day 8	Day 31	Day 38	Day 61	Day 151	Day 211	
Informed consent	●							Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details
Check inclusion/exclusion criteria	●		○					Prior to administering each study intervention, the investigator must check eligibility criteria for subsequent vaccinations and criteria for delay of study intervention administration. See Sections 5.1 and 5.2 for inclusion and exclusion criteria
Study group and treatment number allocation (randomisation)	●							See Section 6.3 for more information
Treatment number allocation for subsequent doses			○					
Collect demographic data	●							See Section 8.2.1.1 for more information
Medical and vaccination history	●							See Section 8.2.1.2 for more information
General physical examination	○							Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information
Symptom-directed physical examination		○	○		○			
Check contraindications, warnings and precautions to study intervention administration	○		○					See Sections 7.1.1 and 8.2.1.5 for more information
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○	○	○		○			See Section 5.5 for more information
Urine pregnancy test for females	●		●					See Section 8.2.1.4 for more information

Type of contact	Visit	Visit	Visit	PC	Visit	PC	PC	Notes
Visit/Phone call no.	V1	V2	V3	T1	V4	T2	T3	
Timepoint(s) [refer to Table 2 for visit windows]	Day 1	Day 8	Day 31	Day 38	Day 61	Day 151	Day 211	
Body temperature before study intervention administration	●		●					Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF
Blood sampling for sourcing	●^		●^		●			Blood volume of approximately 80 mL will be collected at each blood sampling visit. See Section 8.1.1.1 for more information
Blood sampling for safety laboratory evaluation	●^	●						Blood volume of ~7 mL will be collected. See Section 8.1.1.1 for more information
Study intervention administration	●		●					See Section 6.1 for more information
Recording of administered study intervention number	●		●					
Post-injection assessment (30 minutes)	●		●					See Section 10.3.8.1 for more information
Distribution of eDiary	○		○					
Review of eDiary		●	●	●	●			
Return of eDiary					●			
Recording of solicited AEs (Days 1–7 post-vaccination)	x		x					See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1-30 post-vaccination)*	●	●	●	●	●			See Section 10.3.8 for more information
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered See Section 6.8 for more information
Record any intercurrent medical conditions*		●	●	●	●	●	●	See Section 9.3.1 for more information
Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs*	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/ vaccine	●	●	●	●	●	●	●	Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end. See Section 10.3.8 for more information
Study (Phase I) Conclusion							●	Participants who terminate the study early are recommended to complete certain study-related procedures. See Section 4.4 and 10.1.9.1 for more information

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents
× is used to indicate a study procedure that will be documented in the eDiary
^ Procedure to be performed prior to study intervention administration
Abbreviation: PC, phone contact; V, clinic visit; T, telephone call; AE, adverse event; SAE, serious adverse event; AESI, adverse events of special interest. Note: All procedures to be performed prior to study intervention administration (as applicable). The study timepoints are the same for all groups, irrespective of the staggered enrolment (See Section 8.2.2.1).
* Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 10.3 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 34). In addition, separate COVID-19 specific eCRF form(s) should be completed
Note: Refer to Section 8 for information on study procedures during special circumstances

Table 2 Intervals between study visits/contacts –Phase I

Interval	Planned visit/ phone call interval	Allowed interval range (visit window)
Visit V1 → Visit V2	7 days	6 to 8 days (-1 to +1 days)
Visit V1 → Visit V3	30 days	44 days (+14 days)
Visit V3 → Telephone contact T1	7 days	6 to 8 days (-1 to +1 days)
Visit V3 → Visit V4	30 days	25 to 44 days (-5 to +14 days)
Visit V3 → Telephone contact T2	120 days	113 to 134 days (-7 to +14 days)
Visit V3 → Telephone contact T3	180 days	173 to 194 days (-7 to +14 days)

Table 3 Schedule of activities – Phase II (Formulation and schedule-finding)

Type of contact	Visit	PC	Visit	PC	Visit	PC	Visit	Visit	PC	PC	PC	Visit	Notes
Visit/Phone call no.	V1	T1	V2	T2	V3†	TC††	V4	V5	T3	T4	T5	V6	
Timepoint(s) [refer to Table 4 for visit windows]	Day 1	Day 8	Day 31	Day 91	Day 121	Day 121	Day 181	Day 211	Day 271	Day 361	Day 451	Day 541	
Groups	All	First 45**	All	All	ABCWY groups	Control group	All	All	All	All	All	All	
Informed consent	●												Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details
Informed assent, if applicable	○												Confirm assent form (if applicable) signed prior to any procedures
Check inclusion/exclusion criteria	●				○		○						Prior to administering each study intervention the investigator must check eligibility criteria for subsequent vaccination and criteria for delay of study intervention administration See Sections 5.1 and 5.2 for inclusion and exclusion criteria
Study group and treatment number allocation (randomisation)	●												See Section 6.3 for more information
Treatment number allocation for subsequent doses					○		○						
Collect demographic data	●												See Section 8.2.1.1 for more information
Medical and vaccination history	●												See Section 8.2.1.2 for more information
General physical examination	○												Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information
Symptom-directed physical examination			○		○		○	○				○	
Check contraindications, warnings and precautions to study intervention administration	○				○		○						See Sections 7.1.1 and 8.2.1.5 for more information
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○		○		○		○	○				○	See Section 5.5 for more information

Type of contact	Visit	PC	Visit	PC	Visit	PC	Visit	Visit	PC	PC	PC	Visit	Notes
Visit/Phone call no.	V1	T1	V2	T2	V3†	TC††	V4	V5	T3	T4	T5	V6	
Timepoint(s) [refer to Table 4 for visit windows]	Day 1	Day 8	Day 31	Day 91	Day 121	Day 121	Day 181	Day 211	Day 271	Day 361	Day 451	Day 541	
Groups	All	First 45**	All	All	ABCWY groups	Control group	All	All	All	All	All	All	
Urine pregnancy test for females of childbearing potential	●				●		●						See Section 8.2.1.4 for more information
Body temperature before study intervention administration	●				●		●						Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF
Blood sampling	●^		●					●				●	Blood volume of approximately 15 mL will be collected at V1 (pre-vaccination) and V2 and approximately 30 mL at V5 and V6. See Section 8.1.1.1 for more information
Study intervention administration	●				●		●						See Section 6.1 for more information
Recording of administered study intervention number	●				●		●						
Post-injection assessment (30 minutes)	●				●		●						See Section 10.3.8.1 for more information
Distribution of eDiary	○				○		○						
Review of eDiary		●	●				●‡	●					
Return of eDiary								●					
Recording of solicited AEs (Days 1–7 post-vaccination)	x				x		x						See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●	●	●		●		●	●					See Section 10.3.8 for more information
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●	●	●	●	Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered. See Section 6.8 for more information
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●	See Section 9.3.1 for more information
Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs*	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information

Type of contact	Visit	PC	Visit	PC	Visit	PC	Visit	Visit	PC	PC	PC	Visit	Notes
Visit/Phone call no.	V1	T1	V2	T2	V3†	TC††	V4	V5	T3	T4	T5	V6	
Timepoint(s) [refer to Table 4 for visit windows]	Day 1	Day 8	Day 31	Day 91	Day 121	Day 121	Day 181	Day 211	Day 271	Day 361	Day 451	Day 541	
Groups	All	First 45**	All	All	ABCWY groups	Control group	All	All	All	All	All	All	
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	●	Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end. See Section 10.3.8 for more information
Study Conclusion												●	Participants who terminate the study early are recommended to complete certain study-related procedures See Section 4.4 and 10.1.9.1 for more information

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents.
× is used to indicate a study procedure that will be documented in eDiary.
^ Procedure to be performed prior to study intervention administration
Abbreviation: PC, phone contact; V, clinic visit; T, telephone call; TC, Telephone call for Control group only; AE, adverse event; SAE, serious adverse event; AESI, adverse events of special interest.
Note: All procedures to be performed prior to study intervention administration (as applicable). The study timepoints are the same for all groups, irrespective of the staggered enrolment (See Section 8.2.2.1)
* Diagnosis of COVID-19 should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 10.3 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 35). In addition, separate COVID-19 specific eCRF form(s) should be completed.
** The phone call at Day 8 is only for the first 45 participants (15 participants in C , 5 participants in C , 15 participants in C , 5 participants in C and 5 participants in the Control groups). Refer to Section 4.1.2.1 and *Figure 2* for details.
† Visit V3 (at Day 121) is only applicable for C groups
†† TC (at Day 121) is only applicable for the Control group
‡ Not applicable for Control group
Note 1: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Details of how these visits will be conducted are outlined in the study procedure manual (SPM). Refer to Section 8 (decentralised study procedures) for details
Note 2: Refer to Section 8 for information on study procedures during special circumstances

Table 4 Intervals between study visits/contacts –Phase II (Formulation and schedule-finding)

Interval	Planned visit interval	Allowed interval range
Visit V1 → Telephone contact T1*	7 days	6 to 8 days (-1 to +1 days)
Visit V1 → Visit V2	30 days	25 to 44 days (-5 to +14 days)
Visit V1 → Telephone contact T2	90 days	83 to 104 days (-7 to +14 days)
Visit V2 → Visit V3/TC**	90 days	85 to 104 days (-5 to +14 days)
Visit V3/TC** → Visit V4	60 days	55 to 74 days (-5 to +14 days)
Visit V4 → Visit V5	30 days	25 to 44 days (-5 to +14 days)
Visit V4 → Telephone contact T3	90 days	83 to 104 days (-7 to +14 days)
Visit V4 → Telephone contact T4	180 days	173 to 194 days (-7 to +14 days)
Visit V4 → Telephone contact T5	270 days	263 to 284 days (-7 to +14 days)
Visit V4 → Visit V6	360 days	353 to 374 days (-7 to +14 days)

T, Telephone contact; TC, Telephone contact for Control group only

* The phone call (T1) at Day 8 is only for the first 45 participants (15 participants in C , 5 participants in C , 15 participants in C , 5 participants in C and 5 participants in the Control groups).

** Visit for C groups (Visit V3) and telephone call for Control group (TC)

Table 5 Schedule of Activities – Phase II (Sourcing; *0, 1 month vaccination schedule*)

(Amended 22 March 2022)

Type of contact	Visit	Visit	Visit	PC	PC	Notes
Visit/Phone call no.	V1	V2	V3	T1	T2	
Timepoint(s) [refer to Table 8 for visit windows]	Day 1	Day 31	Day 61	Day 151	Day 211	
Informed consent	●					Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details
Check inclusion/exclusion criteria	●	○				Prior to administering each study intervention, the investigator must check eligibility criteria for subsequent vaccinations and criteria for delay of study intervention administration. See Sections 5.1 and 5.2 for inclusion and exclusion criteria
Study group and treatment number allocation (randomisation)	●					See Section 6.3 for more information
Treatment number allocation for subsequent doses		○				
Collect demographic data	●					See Section 8.2.1.1 for more information
Medical and vaccination history	●					See Section 8.2.1.2 for more information
General physical examination	○					Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information
Symptom-directed physical examination		○	○			

Type of contact	**Visit**	**Visit**	**Visit**	**PC**	**PC**	**Notes**
Visit/Phone call no.	**V1**	**V2**	**V3**	**T1**	**T2**	
Timepoint(s) [refer to Table 8 for visit windows]	**Day 1**	**Day 31**	**Day 61**	**Day 151**	**Day 211**	
Check contraindications, warnings and precautions to study intervention administration	○	○				See Sections 7.1.1 and 8.2.1.5 for more information
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○	○	○			See Section 5.5 for more information
Urine pregnancy test for females	●	●				See Section 8.2.1.4 for more information
Body temperature before study intervention administration	●	●				Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF
Blood sampling	●^	●^	●			Blood volume of approximately 95 mL will be collected at each blood sampling visit. See Section 8.1.1.1 for more information
Study intervention administration	●	●				See Section 6.1 for more information
Recording of administered study intervention number	●	●				
Post-injection assessment (30 minutes)	●	●				See Section 10.3.8.1 for more information
Distribution of eDiary	○					
Review of eDiary		●	●			
Return of eDiary			●			
Recording of solicited AEs (Days 1–7 post-vaccination)	**x**	**x**				See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●	●	●			See Section 10.3.8 for more information
Record any concomitant medications/vaccinations	●	●	●	●	●	Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered See Section 6.8 for more information
Record any intercurrent medical conditions		●	●	●	●	See Section 9.3.1 for more information
Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs*	●	●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/ vaccine	●	●	●	●	●	Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end. See Section 10.3.8 for more information
Study (Phase II, Sourcing) Conclusion					●	Participants who terminate the study early are recommended to complete certain study-related procedures. See Section 4.4 and 10.1.9.1 for more information

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents
× is used to indicate a study procedure that will be documented in the eDiary

^ Procedure to be performed prior to study intervention administration
Abbreviation: PC, phone contact; V, clinic visit; T, telephone call; AE, adverse event; SAE, serious adverse event; AESI, adverse events of special interest. Note: All procedures to be performed prior to study intervention administration (as applicable).
* Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 10.3 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 36). In addition, separate COVID-19 specific eCRF form(s) should be completed
Note 1: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details
Note 2: Refer to Section 8 for information on study procedures during special circumstances

Table 6 Schedule of Activities – Phase II (Sourcing; 0, 2 month vaccination schedule)

(Amended 22 March 2022)

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 9 for visit windows]	*Day 1*	*Day 31*	*Day 61*	*Day 76*	*Day 91*	*Day 181*	*Day 241*	
Informed consent	●							*Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details*
Check inclusion/exclusion criteria	●		○					*Prior to administering each study intervention, the investigator must check eligibility criteria for subsequent vaccinations and criteria for delay of study intervention administration. See Sections 5.1 and 5.2 for inclusion and exclusion criteria*
Study group and treatment number allocation (randomisation)	●							*See Section 6.3 for more information*
Treatment number allocation for subsequent doses			○					
Collect demographic data	●							*See Section 8.2.1.1 for more information*
Medical and vaccination history	●							*See Section 8.2.1.2 for more information*
General physical examination	○							*Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information*
Symptom-directed physical examination			○	○	○			

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 9 for visit windows]	*Day 1*	*Day 31*	*Day 61*	*Day 76*	*Day 91*	*Day 181*	*Day 241*	
Check contraindications, warnings and precautions to study intervention administration	○		○					*See Sections 7.1.1 and 8.2.1.5 for more information*
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○		○	○	○			*See Section 5.5 for more information*
Urine pregnancy test for females	●		●					*See Section 8.2.1.4 for more information*
Body temperature before study intervention administration	●		●					*Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF*
Blood sampling	●^			●	●			*Blood volume of approximately 95 mL will be collected at each blood sampling visit.* *See Section 8.1.1.1 for more information*
Study intervention administration	●		●					*See Section 6.1 for more information*
Recording of administered study intervention number	●		●					
Post-injection assessment (30 minutes)	●		●					*See Section 10.3.8.1 for more information*
Distribution of eDiary	○							
Review of eDiary		●		●	●			
Return of eDiary					●			
Recording of solicited AEs (Days 1–7 post-vaccination)	*x*		*x*					*See Section 10.3.8 for more information*
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●	●	●	●	●			*See Section 10.3.8 for more information*
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	*Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered* *See Section 6.8 for more information*
Record any intercurrent medical conditions		●	●	●	●	●	●	*See Section 9.3.1 for more information*
*Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs**	●	●	●	●	●	●	●	*See Section 10.3.8 for more information*
Recording of SAEs related to study participation, or to a concurrent GSK medication/ vaccine	●	●	●	●	●	●	●	*Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end.* *See Section 10.3.8 for more information*

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 9 for visit windows]	*Day 1*	*Day 31*	*Day 61*	*Day 76*	*Day 91*	*Day 181*	*Day 241*	
Study (Phase II, Sourcing) Conclusion							●	*Participants who terminate the study early are recommended to complete certain study-related procedures. See Section 4.4 and 10.1.9.1 for more information*

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents
× is used to indicate a study procedure that will be documented in the eDiary
^ Procedure to be performed prior to study intervention administration
Abbreviation: PC, phone contact; V, clinic visit; T, telephone call; AE, adverse event; SAE, serious adverse event; AESI, adverse events of special interest. Note: All procedures to be performed prior to study intervention administration (as applicable).
** Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 10.3 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 36). In addition, separate COVID-19 specific eCRF form(s) should be completed*
Note 1: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details
Note 2: Refer to Section 8 for information on study procedures during special circumstances

Table 7 Schedule of Activities – Phase II (Sourcing; 0, 6 month vaccination schedule)

(Amended 22 March 2022)

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 10 for visit windows]	*Day 1*	*Day 31*	*Day 181*	*Day 196*	*Day 211*	*Day 301*	*Day 361*	
Informed consent	●							*Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details*
Check inclusion/exclusion criteria	●		○					*Prior to administering each study intervention, the investigator must check eligibility criteria for subsequent vaccinations and criteria for delay of study intervention administration. See Sections 5.1 and 5.2 for inclusion and exclusion criteria*
Study group and treatment number allocation (randomisation)	●							*See Section 6.3 for more information*
Treatment number allocation for subsequent doses			○					
Collect demographic data	●							*See Section 8.2.1.1 for more information*
Medical and vaccination history	●							*See Section 8.2.1.2 for more information*
General physical examination	○							*Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information*
Symptom-directed physical examination			○	○	○			
Check contraindications, warnings and precautions to study intervention administration	○		○					*See Sections 7.1.1 and 8.2.1.5 for more information*
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○		○	○	○			*See Section 5.5 for more information*
Urine pregnancy test for females	●		●					*See Section 8.2.1.4 for more information*
Body temperature before study intervention administration	●		●					*Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF*

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 10 for visit windows]	*Day 1*	*Day 31*	*Day 181*	*Day 196*	*Day 211*	*Day 301*	*Day 361*	
Blood sampling	●^			●	●			*Blood volume of approximately 95 mL will be collected at each blood sampling visit. See Section 8.1.1.1 for more information*
Study intervention administration	●		●					*See Section 6.1 for more information*
Recording of administered study intervention number	●		●					
Post-injection assessment (30 minutes)	●		●					*See Section 10.3.8.1 for more information*
Distribution of eDiary	○							
Review of eDiary		●		●	●			
Return of eDiary					●			
Recording of solicited AEs (Days 1–7 post-vaccination)	x		x					*See Section 10.3.8 for more information*
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●	●	●	●	●			*See Section 10.3.8 for more information*
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	*Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered See Section 6.8 for more information*
Record any intercurrent medical conditions		●	●	●	●	●	●	*See Section 9.3.1 for more information*
*Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs**	●	●	●	●	●	●	●	*See Section 10.3.8 for more information*
Recording of SAEs related to study participation, or to a concurrent GSK medication/ vaccine	●	●	●	●	●	●	●	*Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end. See Section 10.3.8 for more information*
Study (Phase II, Sourcing) Conclusion							●	*Participants who terminate the study early are recommended to complete certain study-related procedures. See Section 4.4 and 10.1.9.1 for more information*

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents
× is used to indicate a study procedure that will be documented in the eDiary
^ Procedure to be performed prior to study intervention administration
Abbreviation: PC, phone contact; V, clinic visit; T, telephone call; AE, adverse event; SAE, serious adverse event; AESI, adverse events of special interest. Note: All procedures to be performed prior to study intervention administration (as applicable).
** Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 10.3 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 36). In addition, separate COVID-19 specific eCRF form(s) should be completed*

Note 1: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details
Note 2: Refer to Section 8 for information on study procedures during special circumstances

Table 8 Intervals between study visits/contacts – Phase II (Sourcing; *0, 1 month vaccination schedule)*

(Amended 22 March 2022)

Interval	Planned visit interval	Allowed interval range (visit window)
Visit V1 → Visit V2	30 days	44 days (+14 days)
Visit V2 → Visit V3	30 days	25 to 44 days (-5 to +14 days)
Visit V2 → Telephone contact T1	120 days	113 to 134 days (-7 to +14 days)
Visit V2 → Telephone contact T2	180 days	173 to 194 days (-7 to +14 days)

Table 9 Intervals between study visits/contacts – Phase II (Sourcing; 0, 2 month vaccination schedule)

(Amended 22 March 2022)

Interval	*Planned visit interval*	*Allowed interval range (visit window)*
Visit 1 → Telephone contact T1	*30 days*	*23 to 44 days (-7 to +14 days)*
Visit V1 → Visit V2	*60 days*	*74 days (+14 days)*
Visit V2 → Visit V3	*15 days*	*10 to 22 days (-5 to +7 days)*
Visit V2 → Visit V4	*30 days*	*25 to 51 days (-5 to +21 days)*
Visit V2 → Telephone contact T2	*120 days*	*113 to 134 days (-7 to +14 days)*
Visit V2 → Telephone contact T3	*180 days*	*173 to 194 days (-7 to +14 days)*

Table 10 Intervals between study visits/contacts – Phase II (Sourcing; 0, 6 month vaccination schedule)

(Amended 22 March 2022)

Interval	*Planned visit interval*	*Allowed interval range (visit window)*
Visit 1 → Telephone contact T1	*30 days*	*23 to 44 days (-7 to +14 days)*
Visit V1 → Visit V2	*180 days*	*194 days (+14 days)*
Visit V2 → Visit V3	*15 days*	*10 to 22 days (-5 to +7 days)*
Visit V2 → Visit V4	*30 days*	*25 to 51 days (-5 to +21 days)*
Visit V2 → Telephone contact T2	*120 days*	*113 to 134 days (-7 to +14 days)*
Visit V2 → Telephone contact T3	*180 days*	*173 to 194 days (-7 to +14 days)*

2. INTRODUCTION

2.1. Study rationale

Neisseria meningitidis infections causing invasive meningococcal disease (IMD) are an important public health concern worldwide due to the substantial morbidity and mortality they cause, as well as the transmissibility of these infections. Ninety percent of meningococcal meningitis and septicaemia are caused by only 5 *N. meningitidis* serogroups: A, B, C, W and Y.

GSK has 2 established meningococcal vaccines against serogroups A, C, W, Y and B respectively, the quadrivalent meningococcal ACWY conjugate vaccine (*Menveo*) and the multi-component recombinant meningococcal B vaccine (*Bexsero*). The availability of a pentavalent meningococcal vaccine in a single administration would however reduce the number of injections, allow greater flexibility in dose administration schedules and increase the coverage for meningococcal disease caused by these serogroups worldwide.

C [redacted]

The CCI drug component as well as the final pentavalent CCI [redacted] have undergone pre-clinical testing in mice, rats and rabbits, to assess immunogenicity and breadth of MenB strain coverage, while a GLP toxicology study to assess local tolerability and systemic toxicity has been concluded. Results from the pre-clinical testing and toxicology study were favourable. Please refer to the current Investigator's Brochure (IB) for information regarding the formulation and pre-clinical studies of CCI vaccine.

The early clinical development plan consists of a seamless Phase I/II study. The first-time-in-human (FTIH), Phase I part of this study will be conducted in healthy adults in a dose-escalating fashion with 2 formulations of the investigational CCI [redacted] referred to hereafter as C [redacted] respectively, and will serve as a safety lead-in to the Phase II study part.

The Phase II part of the study will be conducted in 2 parts: the 'formulation and schedule-finding' part will follow in healthy adolescents and young adults and it is designed to select the vaccine formulation and the schedule to be tested in Phase III. The 'blood sourcing' part will be conducted in healthy adults in order to collect sufficient serum samples for the development of assays to be used in the CCI vaccine clinical development program. Phase II will assess the safety, the effectiveness and the immunogenicity of the above 2 formulations of the investigational CCI

vaccine. *Bexsero* (rMenB+OMV NZ, hereafter referred to as MenB) and *Menveo* (hereafter referred to as MenACWY) will be administered as control vaccines for assessing the response to serogroups B and ACWY, respectively.

2.2. Background

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

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

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

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

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

The Meningococcal Group B Vaccine (*Bexsero*) contains 3 recombinant proteins [factor H binding protein (fHbp), Neisseria adhesin A (NadA), and Neisserial Heparin Binding Antigen (NHBA)], combined with Outer Membrane Vesicles (OMV) components from

the New Zealand outbreak strain NZ98/254. *Bexsero* is immunogenic against the majority of circulating meningococcal serogroup B strains and has acceptable reactogenicity and safety profiles when administered to individuals across age groups. The vaccine is currently approved in more than 40 countries worldwide. Although the meningococcal group B vaccine was developed for individuals aged 2 months and older, the actual age range for which this recommendation extends varies depending on the approval from different health authorities.

Please refer to the current IB for information regarding pre-clinical studies of CCI vaccine.

2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events of CCI vaccine can be found in the IB.

Detailed information about the known and expected benefits and risks and expected adverse events of *Bexsero* (MenB) and *Menveo* (MenACWY) vaccine can be found in the Prescribing Information or Summary of Product Characteristics.

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 (as per the phase in which they are participating: Visit V1 and Visit V3 in Phase I, Visit V1, Visit V3^ and Visit V4 in Phase II Formulation and Schedule-Finding and Visit V1 and Visit V2 in Phase II Sourcing). Refer to Section 6.1.

^ except for Control group participants who will have a phone call at this time point (TC).

In terms of study procedures, blood sampling is associated with a risk of syncope, dizziness, local reactions and infection after or during venepuncture. For this reason, blood samples in this study will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the Informed Consent Form.

Benefit considerations include:

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

Overall Benefit: Risk conclusion

Considering the measures taken to minimise risk to participants participating in this study and since CCI vaccine is based on 2 of GSK's meningococcal vaccines,

Menveo and *Bexsero*, with well-established safety profiles, the potential risks associated with it are justified by the anticipated benefits that may be afforded to participants receiving CCI vaccine.

3. OBJECTIVES AND ENDPOINTS

Table 11 Study objective(s) and endpoints

(Amended 22 March 2022)

Objectives	Endpoints
Phase I – Safety lead-in, Dose escalation	
Primary	
To evaluate the safety and reactogenicity of the 2 formulations (CCI) of the CCI vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at Day 1 and Day 31 in all groups. • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at Day 1 and Day 31 in all groups. • The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 211). • The frequencies and percentages of participants with haematological and biochemical laboratory abnormalities, and changes from the baseline values, after the first vaccination at Day 8, in all groups.
Phase II – Formulation and Schedule-finding	
Primary	
To demonstrate the superiority of the effectiveness of the CCI vaccine (CCI) when administered at 0,2- or 0,6-months schedule, compared to the MenB vaccine administered at 0,6-months schedule*.	The percentages of samples with bactericidal serum activity using enc-hSBA against a panel of 110 randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains at 1 month after the last vaccination (Day 211, Month 7) in all groups.
To demonstrate the immunological non-inferiority of the CCI vaccine CCI) administered at 0,2- or 0,6-months schedule compared to the MenACWY vaccine (single dose)*;†.	The percentages of participants achieving a 4-fold rise** in hSBA titres against serogroups A, C, W and Y at 1 month after the • last CCI vaccination (Day 211, Month 7) for the ABCWY groups and, • MenACWY vaccination (Day 31, Month 1) in the Control group, relative to Day 1, Month 0 in C, C and Control groups and relative to 3 months pre-first CCI vaccination (Day 31, Month 1) in C groups.

Objectives	Endpoints

To evaluate the safety and reactogenicity of the CCI vaccine (CCI), the MenB vaccine and the MenACWY vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at:
	  • Day 1, Day 121 and Day 181 in the C groups, and
	  • Day 1 and Day 181 in the Control group.
	• The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at:
	  • Day 1, Day 121 and Day 181 in the C groups, and
	  • Day 1 and Day 181 in the Control group.
	• The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 541).

Phase II –Sourcing	
Primary	

To evaluate the safety and reactogenicity of the 2 formulations (CCI) of the CCI vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at:
	  • Day 1 and Day 31 in C ***groups,***
	  • ***at Day 1 and Day 61 in*** C ***groups, and***
	  • ***at Day 1 and Day 181 in*** C ***groups.***
	• The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at:
	  • Day 1 and Day 31 C ***groups,***
	  • ***at Day 1 and Day 61 in*** C ***groups, and***
	  • ***at Day 1 and Day 181 in*** C ***groups***.
	• The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period***:***
	  • Day 1 through Day 211 ***in*** C ***and***

Objectives	Endpoints
	C ***groups,*** • ***Day 1 through Day 241 in*** C ***groups, and*** • ***Day 1 through Day 361 in*** C ***groups***).
Phase II – Formulation and Schedule-finding	
Secondary	
To describe the distribution of participants by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the last vaccination of the CCI vaccine (CCI) administered at 0,2 and 0,6-months schedule and of the MenB vaccine administered at 0,6-months schedule.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each participant sample at 1 month after the last vaccination (Day 211, Month 7) in all groups.
To assess the immune response to the CCI vaccine (CCI) administered at 0,2 and 0,6-months schedule and to the MenB vaccine administered at 0,6-months schedule against serogroup B indicator strains.	• The percentages of participants with hSBA titres ≥LLOQ for each and all serogroup B indicator strains at: ○ Day 1, Month 0 in C and Control groups, ○ 3 months pre-first CCI vaccination (Day 31, Month 1) in C groups and, ○ 1 month after the last vaccination (Day 211, Month 7) for all study groups. • The percentages of participants with 4-fold rise in hSBA titres** at 1 month after the last vaccination for all study groups (Day 211, Month 7), relative to: ○ Day 1, Month 0 for C and Control groups and, ○ 3 months pre-first CCI vaccination (Day 31, Month 1) for C groups. • hSBA GMTs against serogroup B indicator strains at: ○ Day 1, Month 0 in C and Control groups, ○ 3 months pre-first CCI vaccination (Day 31, Month 1) in C groups and, ○ 1 month after the last vaccination (Day 211, Month 7) for all study groups. • hSBA GMRs against serogroup B indicator strains at 1 month after the last vaccination (Day 211, Month 7) for all study groups relative to: ○ Day 1, Month 0 for C and Control groups and ○ 3 months pre-first CCI vaccination (Day 31, Month 1) for C groups.
To assess the immune response to the CCI vaccine (CCI) administered at 0,2 and 0,6-months schedule and to the MenACWY vaccine (single dose) against serogroups A, C, W and Y.	• The percentages of participants with hSBA titres ≥LLOQ for serogroups A, C, W and Y at: ○ Day 1, Month 0 in C and Control groups,

Objectives	Endpoints
	○ 3 months pre-first CCI vaccination (Day 31, Month 1) in C groups, ○ 1 month after the first CCI vaccination (Day 31, Month 1) in the C groups, ○ 1 month after the last CCI vaccination (Day 211, Month 7) for all ABCWY groups and, ○ 1 month after the MenACWY vaccination in the Control group (Day 31, Month 1). • The percentages of participants with 4-fold rise in hSBA titres** for serogroups A, C, W and Y at 1 month after the first CCI vaccination (Day 31, Month 1) relative to Day 1, Month 0 for C groups. • hSBA GMTs against serogroups A, C, W and Y at: ○ Day 1, Month 0 in C and Control group, ○ 3 months pre-first CCI vaccination (Day 31, Month 1) in C groups, ○ 1 month after the first CCI vaccination (Day 31, Month 1) in the C groups, ○ 1 month after the last CCI vaccination (Day 211, Month 7) for all ABCWY groups and, ○ 1 month after the MenACWY vaccination in the Control group (Day 31, Month 1). • hSBA GMRs against serogroups A, C, W and Y at 1 month after: ○ the first CCI vaccination (Day 31, Month 1) in the C groups, ○ the last CCI vaccination (Day 211, Month 7) for all ABCWY groups and ○ the MenACWY vaccination in the Control group (Day 31, Month 1), relative to Day 1, Month 0 for C and Control groups and 3 months pre-first CCI vaccination (Day 31, Month 1) for C groups. • The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at: ○ Day 1, Month 0 in C and Control groups, ○ 3 months pre- first CCI vaccination (Day 31, Month 1) in C groups, ○ 1 month after the first CCI vaccination in the C groups and after the MenACWY vaccination in the Control group (Day 31, Month 1) and,

Objectives	Endpoints
	○ 1 month after the last CCI vaccination (Day 211, Month 7) for all ABCWY groups.
Phase II (Formulation and Schedule-finding)	
Tertiary objectives	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

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

Note 1: MenB immune response will be assessed against *N. meningitidis* serogroup B indicator strains CCI [redacted]

Note 2: Evaluation of the tertiary objectives may or not be performed. If the tertiary objectives are evaluated, it may be assessed in a subset of participants using remaining serum after the primary and secondary analyses have been completed; no additional blood samples will be collected from participants.

*All statistical criterion linked to evaluation of the objectives can be found in Section 9.4.

**For the serogroup A C, W, Y and serogroup B evaluations, the 4-fold rise (for serogroup B - per each indicator strain) is defined as:

- -a post-vaccination hSBA titre ≥16 for participants with a pre-vaccination hSBA titre <4,
- -a post-vaccination hSBA titre ≥4 times the LLOQ for participants with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and
- -a post-vaccination hSBA titre ≥4 times the pre-vaccination hSBA titre for participants with a pre-vaccination hSBA titre ≥LLOQ.

† The primary objective of immunological NI of the CCI [redacted] vaccine to MenACWY will be evaluated only in participants without a previous MenACWY vaccination (unprimed). All other primary and secondary objectives will be evaluated in participants with and without previous MenACWY vaccination (primed/unprimed).

CCI [redacted]

4. STUDY DESIGN

(**Amended 22 March 2022**)

4.1. Overall design

This is a seamless Phase I/II multi-country, self-contained study comprising of 2 phases, in order to ensure the safety of participants.

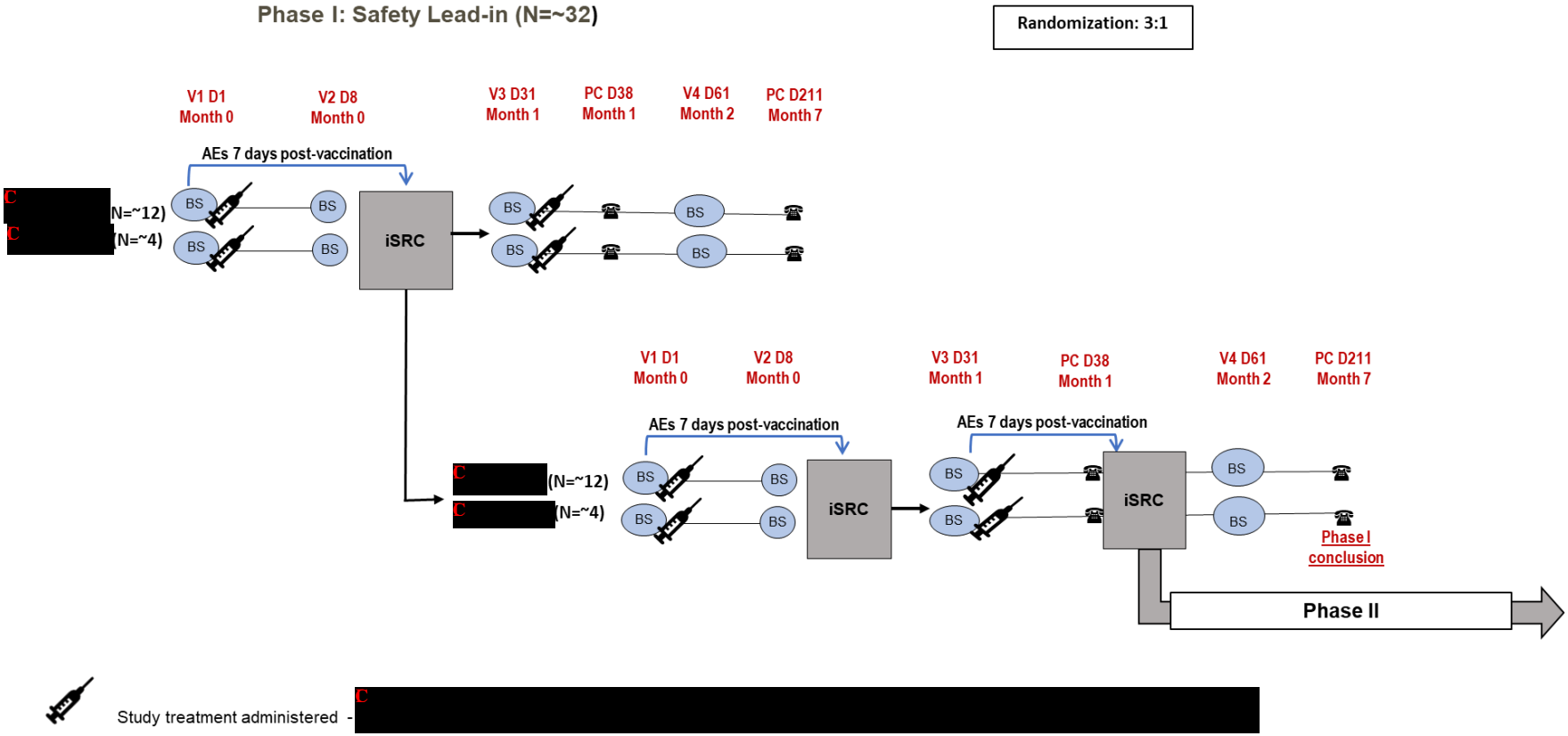
4.1.1. Phase I study design

The Phase I safety lead-in will include 4 study groups (randomised 3:1), with a staggered enrolment (16 participants initially followed by 16 participants later) of a total of 32 participants (Figure 1).

- C Participants will receive the C vaccine in a 0,1-month schedule.
- C: Participants will receive a saline placebo in a 0,1-month schedule, as control group for C
- C: Participants will receive the C vaccine in a 0,1-month schedule.
- C: Participants will receive a saline placebo in a 0,1-month schedule, as control group for C

For more detailed information on study groups and treatments administered, refer to Table 12 and Table 15.

Figure 1 Study design overview – Phase I (Safety Lead-in)



Abbreviation: N, number of participants; V, clinic visit; D, day; iSRC, internal safety review committee; PC, phone contact; BS, blood sample.
Note 1: This figure represents the main aspects of the study design. Refer to Table 1, Schedule of activities, for details on all visits and contacts
Note 2: Refer to Section 8 for information on study procedures during special circumstances.

A GSK internal Safety Review Committee (iSRC, composed of senior GSK experts, independent from the study team) will meet at pre-defined timepoints to perform unblinded review of safety data as described in Section 8.2.2.1.

A total of 16 participants will be randomised with 3:1 ratio to C groups (12 participants in the C group and 4 participants in the C group). A "go-no go" decision will be taken by the iSRC based on safety and reactogenicity data from these participants, as described in Section 8.2.2.1. If the decision is "go", further visits and vaccination for these 2 groups will continue and recruitment of participants in groups C and C will start.

Similarly, a total of 16 participants will be randomised with 3:1 ratio to C groups (12 participants in the C group and 4 participants in the C group). Again, a "go-no go" decision will be taken by the iSRC based on safety and reactogenicity data from these participants. If the decision is "go", further visits and vaccination for these 2 groups will continue. Safety and reactogenicity data from these 2 groups post 2nd dose will be evaluated for a last "go" decision to enable the start of the Phase II.

The schedule of activities in the Phase I is described in Table 1.

Table 12 Study groups, intervention and blinding – Phase I

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
C	12	18-40 yoa	C	Observer-blinded
	12	18-40 yoa		
	4	18-40 yoa	NaCl	
	4	18-40 yoa	NaCl	

Duration of the Phase I of the study: The intended duration of the Phase I of the study, per participant is approximately 7 months.

Data collection: Standardised Electronic Case Report Form (eCRF). Solicited events will be collected using a participant diary (electronic Diary [eDiary]).

Sampling schedule for Phase I of the study:

- Blood sample: Refer to Section 8.1.1.1 for details on collection of blood samples.
- Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential at Visit 1 (Day 1) and Visit 3 (Day 31) prior to the study intervention.

4.1.2. Phase II study design

Phase II will start only after a positive outcome from the iSRC review of the safety data from participants receiving both vaccinations of the higher-dosage vaccine formulation in Phase I of the study. Phase II will be conducted in 2 parts: Formulation and Schedule-finding and Blood sourcing with enrolment commencing parallelly to both these parts.

4.1.2.1. Phase II: Formulation and Schedule-finding

Phase II (Formulation and Schedule-finding) will include 5 study groups, with a staggered enrolment (45 participants for safety lead-in and 955 participants thereafter) of a total of 1000 participants (Figure 2):

- CCI Participants will receive 2 vaccinations of the C vaccine in a (0,6-months) schedule.
- CCI: Participants will receive 2 vaccinations of the C vaccine in a (0,2-months) schedule.
- CCI Participants will receive 2 vaccinations of the C vaccine in a (0,6-months) schedule.
- CCI: Participants will receive 2 vaccinations of the C vaccine in a (0,2-months) schedule.

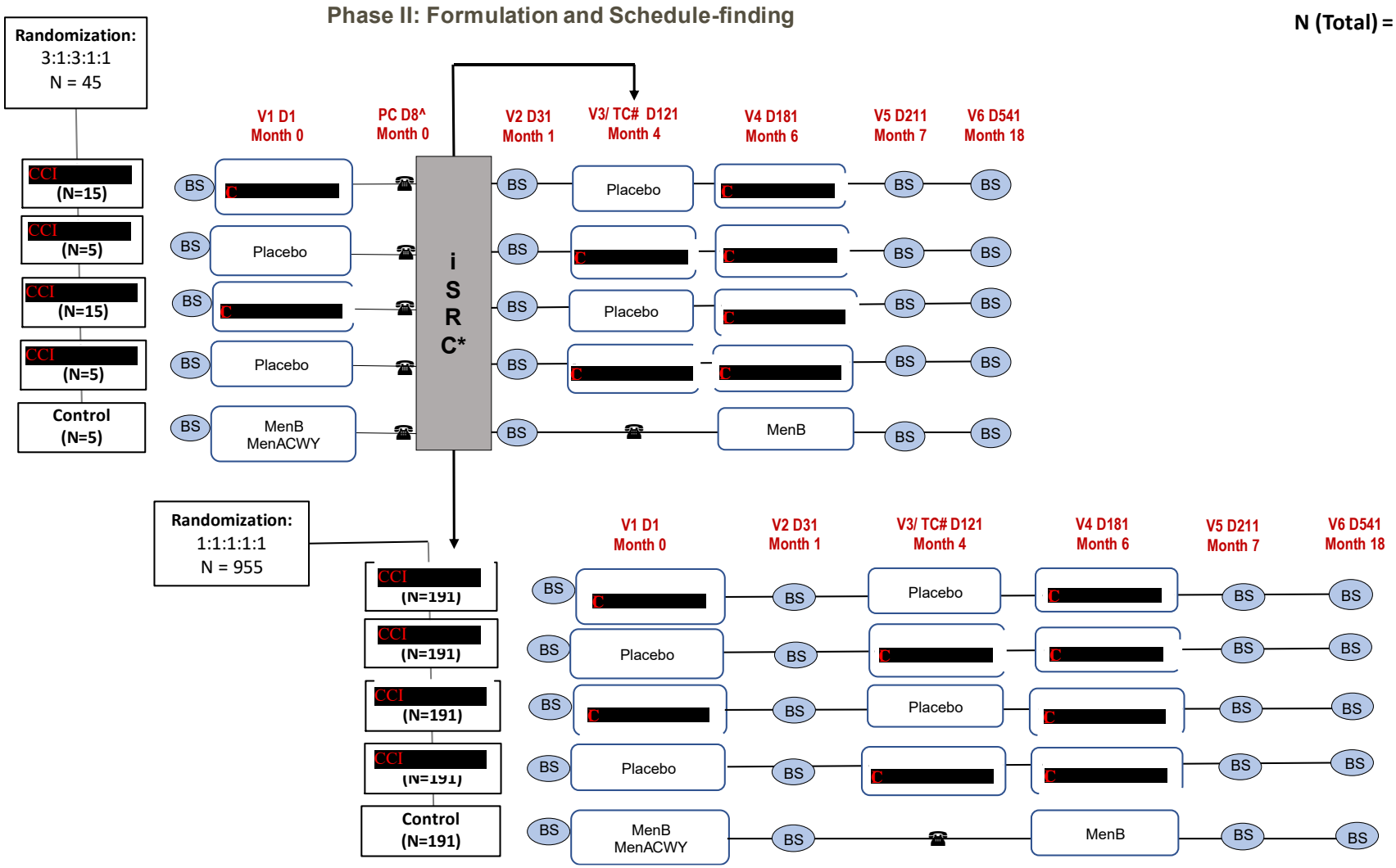
The above 4 groups will also receive 1 injection of placebo, according to the schedule described in Figure 2.

- **Control**: Participants will receive 2 vaccinations of MenB vaccine (*Bexsero*) in a (0,6-months) schedule and a single vaccination of MenACWY vaccine (*Menveo*).

For more detailed information on study groups and treatments administered, refer to Table 13 and Table 16.

The schedule of activities in Phase II (Formulation and Schedule-finding) of the study is described in Table 3.

Figure 2 Study design overview – Phase II (Formulation and Schedule-finding)



Abbreviation: N, number of participants; V, clinic visit; D, day; TC, Telephone contact for Control group only; iSRC, internal safety review committee; PC, phone contact; BS, blood sample.

^ The phone call at Day 8 is only for the first 45 participants (15 participants in CCI, 5 participants in CCI 15 participants in CCI 5 participants in CCI and 5 participants in the Control groups).

* The outcome of the iSRC will impact the next study intervention at Month 4. The Month 1 blood sampling will proceed as planned.

Note 1: Blood draw at Visit 6 Month 18 will be used only for assessment of tertiary objectives.

Note 2: This figure represents the main aspects of the study design. Refer to Table 3 , Schedule of activities, for details on all visits and contacts

Note 3: The Phase II (Formulation and Schedule-finding) is partially blinded. Study conduct and data collection in groups C will be observer-blind while in group Control it will be open-label.

Day 121 Month 4 is a visit for C groups (Visit V3) and is a telephone call for Control group (TC)

Note 4: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Refer to the SoA (Table 3) for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details

Note 5: Refer to Section 8 for information on study procedures during special circumstances.

A total of 45 participants will be randomised with 3:1:3:1:1 ratio to the 5 groups (15 in the C , 5 in the C 15 in the C , 5 in the C and 5 in the Control group). A "go-no go" decision will be taken by the iSRC based on safety and reactogenicity data from these participants (Section 8.2.2.1).

Note: The outcome of the iSRC will impact the next study intervention at Month 4. The Month 1 blood sampling will proceed as planned.

If the decision is "go", further vaccination at Month 4 and other study procedures following that will continue in these groups (as per the study design) along with continuing to recruit participants with a randomisation ratio of 1:1:1:1:1 (191 in each group) to reach the target total sample of 955 participants. Refer to Table 13 for total number of participants per group.

Table 13 Study groups, intervention and blinding – Phase II (Formulation and Schedule-finding)

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
C	206	10 – 25 yoa	C NaCl	Observer-blinded
	196	10 – 25 yoa	C NaCl	
	206	10 – 25 yoa	C NaCl	
	196	10 – 25 yoa	C NaCl	
Control	196	10 – 25 yoa	MenACWY rMenB+OMV NZ	Open-label

Duration of the Phase II (Formulation and Schedule-finding) of the study: The intended duration of the Phase II of the study, per participant is approximately 18 months.

Data collection: standardised eCRF. Solicited events will be collected using a participant diary (eDiary).

Sampling schedule for Phase II (Formulation and Schedule-finding) of the study:

- Blood sample: Refer to Section 8.1.1 for details on collection of blood samples.
- Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential at Visit 1 (Day 1), Visit 3 (Day 121) and Visit 4 (Day 181) prior to the vaccination in the ABCWY groups and at Visit 1 (Day 1) and Visit 4 (Day 181) prior to the vaccination in the Control group.

4.1.2.2. Phase II: Sourcing

(Amended 22 March 2022)

The blood sourcing part of the Phase II study will include 2 groups (randomised 1:1), with a parallel enrolment of a total of 226* participants:

- C : Participants will receive 2 vaccinations of the C vaccine in a (0,1-month) schedule.
- C : Participants will receive 2 vaccinations of the C vaccine in a (0,1-month) schedule.

**** At the time of this protocol amendment (Protocol amendment 4), enrolment to these 2 groups had been stopped. The total number of participants enrolled have been presented in Figure 3.***

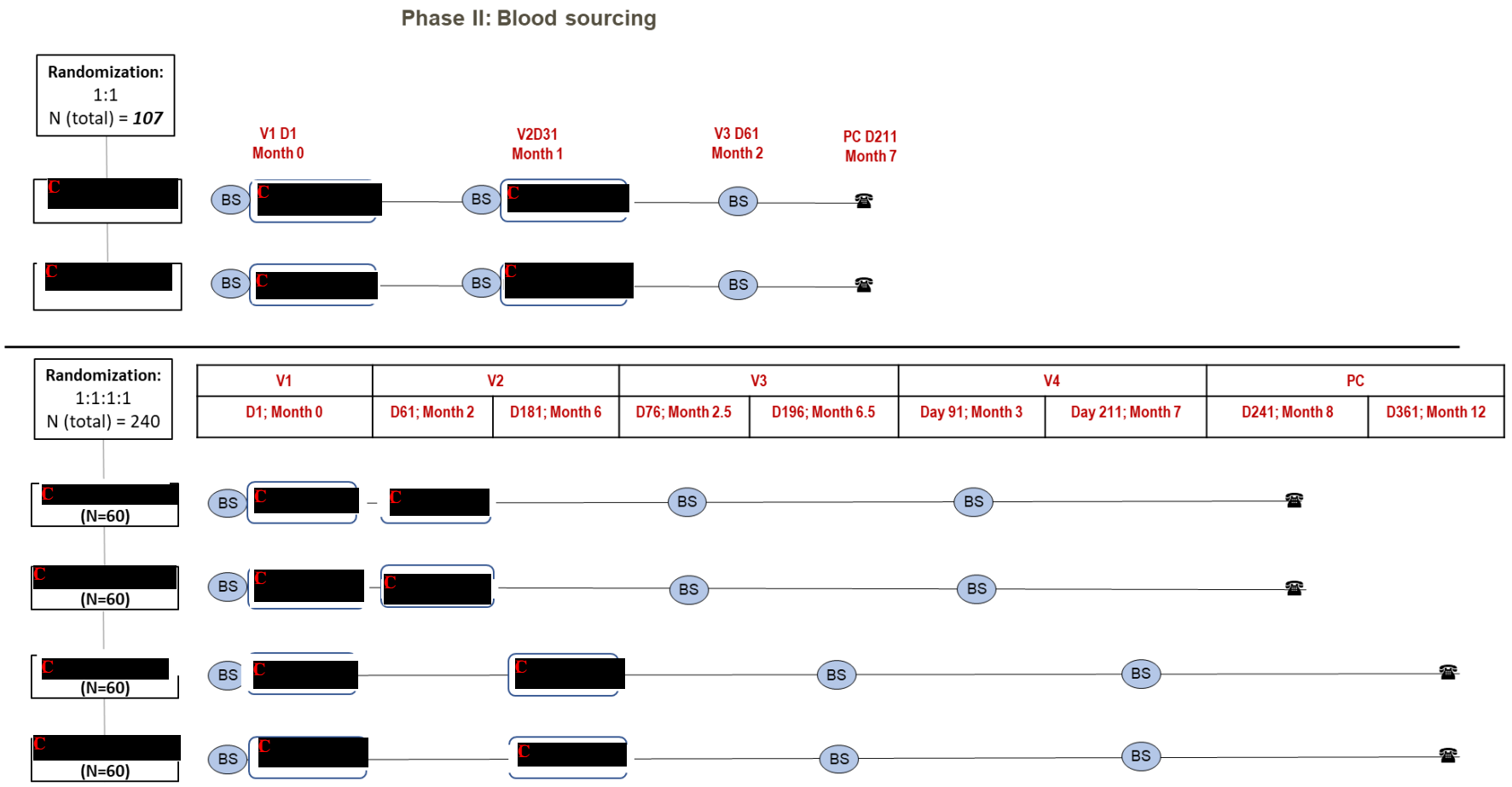
Additionally, the Phase II sourcing part will include 4 more groups (randomised 1:1:1:1), with a parallel enrolment of a total of 240 participants (Figure 3):

- C ***: Participants will receive 2 vaccinations of the*** C ***vaccine in a (0,2-month) schedule.***
- C ***Participants will receive 2 vaccinations of the*** C ***vaccine in a (0,2-month) schedule.***
- C ***: Participants will receive 2 vaccinations of the*** C ***vaccine in a (0,6-month) schedule.***
- C ***: Participants will receive 2 vaccinations of the*** C ***vaccine in a (0,6-month) schedule.***

For more detailed information on study groups and treatments administered, refer to Table 14 and Table 17.

The schedule of activities in the Phase II (sourcing) ***are*** described in Table 5, ***Table 6*** **and** ***Table 7*****.**

Figure 3 Study design overview – Phase II (Sourcing)



Abbreviation: N, number of participants; V, clinic visit; D, day, PC, phone contact; BS, blood sample.
Note 1: This figure represents the main aspects of the study design. Refer to Table 5, ***Table 6 and Table 7***, Schedule of activities, for details on all visits and contacts
Note 2: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Refer to the SoA (Table 5, ***Table 6 and Table 7***) for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details
Note 3: Refer to Section 8 for information on study procedures during special circumstances.

Table 14 Study groups, intervention and blinding – Phase II (Sourcing)

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
C [redacted]	***107***	18-50 yoa	C [redacted]	Observer-blinded*
	60			
	60			
	60			
	60			

**** Due to the different vaccination schedules in Phase II Sourcing, the study will be observer blind only in terms of the vaccine formulations.***

Duration of the Phase II (Sourcing) of the study: The intended duration of the Phase II (sourcing) of the study, per participant is:

- approximately 7 months ***for the*** C [redacted] ***and*** C [redacted] ***groups***,
- ***approximately 8 months for the*** C [redacted] ***and*** C [redacted] ***groups, and,***
- ***approximately 12 months for the*** C [redacted] ***and*** C [redacted] ***groups.***

Data collection: Standardised Electronic Case Report Form (eCRF). Solicited events will be collected using a participant diary (electronic Diary [eDiary]).

Sampling schedule for Phase II (Sourcing) of the study:

- Blood sample: Refer to Section 8.1.1.1 for details on collection of blood samples.
- Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential prior to the study intervention ***(at the following timepoints):***
  - ***at Visit 1 (Day 1) and Visit 2 (Day 31) for the*** C [redacted] ***and*** C [redacted] ***groups,***
  - ***at Visit 1 (Day 1) and Visit 2 (Day 61) for the*** C [redacted] ***and*** C [redacted] ***groups, and,***
  - ***at Visit 1 (Day 1) and Visit 2 (Day 181) for the*** C [redacted] ***and*** C [redacted] ***groups.***

The **primary completion date** for the study is the Day 541, Month 18 timepoint in Phase II. Refer to Section 9.4.6 for the planned interim analysis.

4.2. Scientific rationale for study design

(Amended 22 March 2022)

The investigational CCI vaccine is composed of C [redacted]

As the investigational CCI vaccine has never been administered to humans, the study will follow a staggered design with 2 phases in order to assess the safety of the new vaccine first in a small group of healthy adults 18 through 40 years of age (Phase I), and subsequently in a small group of healthy adolescents and young adults aged 10 through 25 years prior to proceeding with the full enrolment in Phase II.

- The first part of the study [**Phase I** (Figure 1)] will serve as a safety lead-in to the Phase II part of the study.
- The second part of the study [**Phase II** (*Figure 2* ***and Figure 3***] will only commence after demonstration of acceptable safety and reactogenicity in Phase I participants (Section 4.1.1). This Phase II will have 2 components – the formulation and schedule-finding part and the blood sourcing part.

The 0,1-month schedule was selected for Phase I and Phase II (Sourcing) because the short time interval between vaccinations is conservative for the assessment of reactogenicity and safety.

Furthermore, the CCI vaccine will also be administered according to a 0,2month or 0,6month interval (wider dosing schedules) in the Phase II Sourcing part to support the finalization of assay development, further clinical testing, as well as assay stability monitoring and maintenance. For this reason, the total sample size of subjects in the Phase II Sourcing have been increased.

The formulation and schedule-finding part of the Phase II is designed to assess safety, effectiveness and immunogenicity of CCI [redacted]. The 2-dose schedule, as well as the interval between doses are based on the dosing schedule approved for *Bexsero* in adolescents and young adults.

Menveo and *Bexsero* will be administered as comparators in Phase II, in line with the respective approved labels in this age group (CCI [redacted] in Phase I/II.

<u>Rationale for use of placebo:</u>

The placebo treatment (saline solution) is included in this study as:

- a control for safety assessments (in Phase I), and,
- to maintain the blinding (in Phase I and Phase II, Formulation and Schedule-finding).

4.3. Justification for dose

No previous clinical trials have been performed with the GSK CCI vaccine candidate. The development of CCI vaccine leverages the experience gathered from the 2 GSK vaccines on the market, *Bexsero* (MenB vaccine) and *Menveo* (MenACWY vaccine), for which significant amount of non-clinical, clinical and post-marketing data have been generated.

CCI

4.4. End of Study definition

(Amended 22 March 2022)

A participant is considered to have completed the study if he/she returns for the last visit or is available for the last scheduled contact/ visit as described in the protocol ***[***Telephone T3 in Phase I, Visit V6 in Phase II, Formulation and Schedule-finding and Telephone T2 ***or Telephone T3*** in Phase II, Sourcing ***(as per the group allocation)]***.

End of Study (EoS): Date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after Last Subject Last Visit (LSLV) (LSLV = Day 541, Month 18 in Phase II, formulation and schedule-finding). ***If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.***

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardise the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

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

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

All inclusion criteria are applicable for both study phases, except where specified otherwise.

- Participants and/or participants' parent(s)/Legally Acceptable Representative(s) (LAR) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the eDiaries, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the participant or /parent(s)/LAR(s) of the participant prior to performance of any study specific procedure.
- Written informed assent obtained from the participant (if applicable) prior to performing any study specific procedure.
- **Phase I only**: A male or female between, and including, 18 and 40 years of age (i.e. 40 years + 364 days) at the time of the first study intervention administration.
- **Phase II (Formulation and Schedule-finding) only**: A male or female between, and including, 10 and 25 years of age (i.e. 25 years + 364 days) at the time of the first study intervention administration.
- **Phase II (Sourcing) only:** A male or female between, and including, 18 and 50 years of age (i.e. 50 years + 364 days) at the time of the first study intervention administration.
- Participants who are either unvaccinated with MenACWY vaccine or have received a single previous dose of MenACWY vaccine can participate in the study, if they have received it at least 4 years prior to informed consent and assent as applicable (with the exception of meningococcal C vaccination, if the last dose of MenC was received at ≤24 months of age).
- Healthy participants as established by medical history and clinical examination before entering into the study.
- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause. Refer to Section 10.5.1 for definitions of menarche and menopause.

- Female participants of childbearing potential may be enrolled in the study, if the participant:
  - 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 treatment period and for 1 month after completion of the study intervention administration.

  Refer to Section 10.5.1 for definitions of woman of childbearing potential and adequate contraception

5.2. Exclusion criteria

All exclusion criteria are applicable for both study phases, except where specified otherwise**.**

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

5.2.1. Medical conditions

- Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection within 60 days of enrolment.
- Progressive, unstable or uncontrolled clinical conditions.
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
- Are obese at enrolment (e.g. for participants from 20 years of age a body mass index (BMI) $\geq$ 30 kg/m^2, for participants up to 19 years of age a BMI $\geq$ 95th percentile for age and gender or as applicable per country recommendations).
- Any neuroinflammatory (including but not limited to: demyelinating disorders, encephalitis or myelitis of any origin), congenital neurological conditions, encephalopathies, seizures (including all subtypes such as: absence seizures, generalised tonic-clonic seizures, partial complex seizures, partial simple seizures). History of febrile convulsions should not lead to exclusion.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions.
- Hypersensitivity, including allergy, to any component of vaccines, including diphtheria toxoid (CRM_{197}) and latex medicinal products or medical equipment whose use is foreseen in this study.
- Abnormal function or modification of the immune system resulting from:
  - Autoimmune disorders (including, but not limited to: blood, endocrine, hepatic, muscular, nervous system or skin autoimmune disorders; lupus erythematosus

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

- Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 3 months prior to study vaccination until the last blood sampling visit for Phase I and Phase II (Sourcing) and Visit 5 (Day 211) for Phase II (Formulation and Schedule-finding). This will mean prednisone equivalent ≥20 mg/day for adult participants/ ≥0.5 mg/kg/day with maximum of 20 mg/day for paediatric participants. Inhaled and topical steroids are allowed.
- Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to study vaccination.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).

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

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period beginning 30 days before the first dose of study intervention(s) (Day -29 to Day 1), or their planned use during the study period.
- Previous vaccination against any group B meningococcal vaccine at any time prior to informed consent and assent as applicable.
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the administration of the first dose of study intervention(s) or planned administration until the last blood sampling visit for Phase I and Phase II (Sourcing) and Visit 5 (Day 211) for Phase II (Formulation and Schedule-finding).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose(s) until the last blood sampling visit for Phase I and Phase II (Sourcing) and Visit 5 (Day 211) for Phase II (Formulation and Schedule-finding). For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants/ ≥0.5 mg/kg/day with maximum of 20 mg/day for paediatric participants. Inhaled and topical steroids are allowed.

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/invasive medical device).

5.2.4. Other exclusions

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- History of /current chronic alcohol abuse and/or drug abuse as determined by the investigator.
- Any study personnel or immediate dependents, family, or household member.
- **Phase II (Formulation and Schedule-finding)**: Child in care. Please refer to the Glossary of terms for the definition of child in care.

5.3. Lifestyle considerations

Not applicable.

5.4. Screen failures

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

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

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

(Amended 22 March 2022)

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

- Acute disease and/or fever at the time of enrolment and/or study intervention administration. Refer to the SoA for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Significant acute illness within the previous 7 days ***of study intervention administration***.
- Receipt of systemic antibiotics within 3 days prior to blood sampling visit (this will defer blood draw).

- A positive test for current infection with COVID-19 ***prior to intervention administration***. The testing should have been done using a molecular (polymerase chain reaction [PCR] or antigen test) approved by the country regulatory authorities.
- Participants with known COVID-19 positive contacts ***and considered at risk of having contracted a COVID-19 infection according to local regulations***.
- Individuals who have received any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to and following each vaccination up to Visit 3 for Phase I, up to Visit 4 for Phase II (Formulation and Schedule-finding) and up to Visit 2 for Phase II (Sourcing)*.

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

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

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

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study intervention(s) administered

Refer to Section 4 for the study intervention administration schedule.

Table 15 Study intervention administered – Phase I

Study intervention name:	C [redacted]		Placebo
Study intervention formulation†			Sodium chloride (NaCl) (0.9%); Water for injections
Dose Form/ Presentation			Solution for injection /Syringe
Product category	Combination	Combination	Combination
No of doses			
C [redacted]	2	-	-
	-	2	-
	-	-	2
	-	-	2
Volume to be administered^	C [redacted]		
Type	Study	Study	Control
Route of administration	Intramuscular use	Intramuscular use	Intramuscular use

Study intervention name:	[redacted]		**Placebo**
Administration site			
• Location	Deltoid	Deltoid	Deltoid
• Laterality**	Non-dominant	Non-dominant	Non-dominant
Packaging, labelling and TM:	Refer to SPM for details		
Manufacturer:	GSK	GSK	GSK

† The composition per dose is presented here

CCI [redacted]

Table 16 Study intervention administered – Phase II (Formulation and Schedule-finding)

Study intervention	C	***Bexsero***	***Menveo****	**Placebo (saline)**
Formulation†	C			Sodium chloride (NaCl) (0.9%); Water for injections
Dose Form/ Presentation				Solution for injection/ Syringe
Product category	Combination	Combination	Combination	Biological	Combination
C	2	-	-	-	1
	2	-	-	-	1
	-	2	-	-	1
	-	2	-	-	1
Control	-	-	2	1	
Volume to be	CCI				

Study intervention administered^	C [redacted]		***Bexsero***	***Menveo****	**Placebo (saline)**
Type	Study	Study	Control	Control	Concomitant
Route of administration	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use
Administration site					
Location	Deltoid	Deltoid	Deltoid	Deltoid	Deltoid
Laterality***	Non-dominant***	Non-dominant***	Non-dominant***	Dominant	Non-dominant***
Packaging, labelling and TM:	Refer to SPM for details				
Manufacturer:	GSK	GSK	GSK	GSK	GSK

†The composition per dose is presented here.

CCI [redacted]

Table 17 Study intervention administered – Phase II (Sourcing)

(Amended 22 March 2022)

Study intervention name:	C [redacted]	
Study intervention formulation†		
Dose Form/ Presentation		
Product category	Combination	Combination
No of doses		
• C [redacted]	2	-
•	-	2
•	**2**	**-**
•	**-**	**2**
•	**2**	**-**
•	**-**	**2**
Volume to be administered^	CCI [redacted]	
Type	Study	Study
Route of administration	Intramuscular use	Intramuscular use
Administration site		
• Location	Deltoid	Deltoid
• Laterality*	Non-dominant	Non-dominant

Study intervention name:	C	
Packaging, labelling and TM:	Refer to SPM for details	
Manufacturer:	GSK	GSK

† The composition per dose is presented here

CCI

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.

6.2. Preparation/Handling/Storage/Accountability

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

Only authorised study personnel should be allowed access to the study intervention(s). Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the SPM for more details on storage and handling of the study intervention(s).

6.3. Measures to minimise bias: randomisation and blinding

6.3.1. Participant identification

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

6.3.2. Randomisation to study intervention

There are 2 randomisation processes for each participant in the study:

- Randomisation to study intervention

C [redacted]

6.3.3. Intervention allocation to the participant

In Phase I and Phase II (Sourcing), the randomisation algorithm will use a minimisation procedure accounting for the study.

In Phase II (Formulation and Schedule-finding), the minimisation procedure will account for age category (10-17 years of age and 18-25 years of age) and previous MenACWY vaccination (priming) (Yes and No)*.

It is recommended to have a balance between age category during enrolment in Phase II (Formulation and Schedule-finding).

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

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

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

Refer to the SPM for additional information about the study intervention number allocation.

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

6.3.4. Allocation of participants to assay subsets

Refer to Section 9 for details on the allocation as per the MenACWY priming and the analysis planned. Blood samples will be collected as detailed in Section 8.1.1.1. Refer to Section 10.2.1 for details on allocation of participants for safety laboratory assays.

Refer to Section 8.1.3 for details on allocation of participants to assay subsets and Section 10.2.2.1.1 for details on randomisation to strains for enc-hSBA testing.

6.3.5. Blinding and unblinding

(Amended 22 March 2022)

6.3.5.1. Phase I and Phase II (Sourcing)

(Amended 22 March 2022)

Data will be collected in an observer-blind manner. To do so, study intervention(s) will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety, efficacy).

Note: Due to the different vaccination schedules in Phase II Sourcing, the study will be observer blind only in terms of the vaccine formulations

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 and the identity of the participant.

6.3.5.2. Phase II (Formulation and Schedule-finding)

This phase is partially blinded. Data in the 4 ABCWY groups will be collected in an observer-blind manner. To do so, study intervention(s) will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety, efficacy).

Data in the Control group will be collected in an open-label manner i.e. study participants, investigator and site staff personnel will be aware of the treatment administered as 2 study interventions are administered at Visit V1.

The laboratory in charge of the laboratory testing will be blinded to the treatment as well as to the subject number. There will be no link between the study intervention groups and the identity of the participant. In addition, for each sample, a different randomly selected

subject code will be used at each timepoint. This subject coding will prevent the testing laboratory personnel from linking the consecutive timepoints to a specific subject.

Refer to the SPM for additional information about details on study blinding.

6.3.5.3. Unblinding

(Amended 22 March 2022)

The participant, the site and sponsor personnel involved in the clinical evaluation of the participants will be unblinded to the treatment assigned at a Phase at completion of that particular Phase.

Refer to Section 4.4 for the definition of study completion per participant.

6.3.5.4. Emergency unblinding

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

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via SBIR.

The investigator may contact a GSK Helpdesk (refer to the Table 18) if he/she needs help to perform the unblinding process (i.e., if the investigator is unable to access the automated Internet-based system).

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

Table 18 Contact information for emergency unblinding

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

Refer to SPM for country-specific numbers

6.3.5.5. Unblinding prior to regulatory reporting of SAEs

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention(s), prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to the Section 10.3.10.1).

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

6.4. Study intervention compliance

When the study intervention is administered at the site, participants will receive it directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose in the clinic will be recorded in the source documents.

6.5. Dose modification

Not applicable.

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

(Amended 22 March 2022)

During the study conclusion visit/contact (Telephone T3 in Phase I, Visit V6 in Phase II, Formulation and Schedule-finding and Telephone T2***/ Telephone T3*** in Phase II, Sourcing ***[as per group allocation]***), the investigator will ask each participant/participant's parent(s)/LAR(s) if they are interested in participating/allowing the participant to join a booster study/long-term study. If a participant/participant's parent(s)/LAR(s) is/are not interested in joining the booster study/long-term study the reason for refusal will be documented, when available, in the participant's eCRF.

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

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

6.7. Treatment of overdose

Not applicable.

6.8. Concomitant therapy

(Amended 22 March 2022)

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

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

- All concomitant medication associated with an adverse event, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention (Phase 1 and Phase II, Sourcing: Day 1 to Day 211 ***or Day 241 or Day 361 (as per the group allocation)*** and Phase II, Formulation and Schedule-finding: Day 1 to Day 541).
- Any concomitant vaccination administered in the period starting 14 days before the first dose of study intervention and ending at the last study contact (Phase 1 and Phase II, Sourcing: -Day 14 to Day 211 ***or Day 241 or Day 361 (as per the group allocation)*** and Phase II, Formulation and Schedule-finding: Day -14 to Day 541).
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Refer to Sections 5.2.2 and 9.3.1 for details.
- All concomitant medication which may explain/cause/be used to treat SAE/Adverse Event of Special Interest (AESI) including vaccines/products, as defined in Sections 8.3.1 and 10.3.8.2. These must also be recorded in the Expedited Adverse Event Report.
- The use of antipyretic and/or other medications to prevent (prophylactic use) and/or treat fever during the first 7 days after vaccination to be recorded in the eCRF.
- The use of analgesics to prevent (prophylactic use) and/or treat pain during the first 7 days after vaccination to be recorded in the eCRF.
- Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present. An anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [Refer to Table 1, Table 3 and Table 5 for definition of fever].
- The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications eCRF.
- The use of systemic antibiotics within 3 days prior to blood sampling visit is a reason to delay blood sampling (see Section 5.5, Criteria for temporary Delay of Vaccination).

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

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

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

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

7.1.1. Contraindications to subsequent study intervention(s) administration

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

Participants who meet any of the criteria listed below or criteria listed in sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigators' discretion (Section 10.3.8.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Any occurrence of an event listed in the exclusion criteria which must be always re-assessed by the investigator before administration of the next dose of study vaccine.
- Anaphylaxis following the administration of study intervention(s).
- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Any condition that in the judgement of the investigator would make intramuscular injection unsafe.

- Occurrence of a new AESI or the exacerbation of an existing AESI that, in the opinion of the investigator, exposes the participant to unacceptable risk from subsequent doses of study intervention. Refer to Section 10.3.5 for the definition of AESIs.
- Pregnancy (See Section 10.3.7.1).

7.2. Participant discontinuation/withdrawal from the study

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

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

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

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. Refer to Table 1, Table 3 and Table 5 for details.

The primary reason for study withdrawal will be documented in the eCRF, based on the list below. The investigator will document whether the decision to withdraw a participant from the study was made by the participant himself/herself, by the participant's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Adverse events requiring expedited reporting to GSK (Refer to Section 10.3.10.1 for the details)
- Unsolicited non-serious adverse events
- Solicited adverse event
- Withdrawal by participant, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

Participants who are withdrawn from the study because of AEs/SAEs/AESIs/pregnancy 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/AESI/pregnancy until the event is resolved (see Section 10.3.8.2).

A participant will be withdrawn if the participant's treatment code is unblinded by the investigator or treating physician (Refer to Section 6.3.5.4). The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

7.3. Lost to follow-up

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

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

Study conclusion call/visit and discontinuation of individual sites or of the study as a whole is described in Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

All screening evaluations must be completed and the results reviewed before confirming that potential participants meet all eligibility criteria. Refer to Sections 8.2.1.2 and 8.2.1.3 for details on screening evaluations in this study. Note: The safety laboratory evaluations in Phase I are not part of the screening evaluation in this study.

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

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

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

Decentralised study procedures (Phase II only):

If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. telemedicine, home visits) for the collection of biological samples and/or safety data/safety assessment(s)/study intervention administration. These remote visits must be performed by qualified study staff/healthcare professionals HCPs.

Refer to the Schedule of Activities for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM.

Following procedures can be performed remotely/ virtually (with the exception of Visit 1 which is always a clinic visit). Refer to the Glossary of terms for definitions of telemedicine, remote and virtual visits:

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

Study procedures in special circumstances:

(Amended 22 March 2022)

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

- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 4 for Phase I, Visit 5 for Phase II, Formulation and Schedule-finding and Visit 3 for Phase II, Sourcing).
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- Phase II only (not applicable for Visit V1): Study visits may be performed at a different location* other than the study site (e.g. at participant's home). For study visits involving blood draw, biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to collect the biological samples within the interval pre-defined in the protocol (see Table 2 for Phase I, Table 4 for Phase II, Formulation and Schedule-finding and Table 8, ***Table 9 and Table 10*** for Phase II, Sourcing), then the applicable intervals may be extended up to a maximum length of days as presented in Table 19 (Phase I), Table 20 (Phase II, Formulation and

Schedule-finding) and Table 21, ***Table 22 and Table 23*** (Phase II, Sourcing), as applicable.

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Table 2 for Phase I, Table 4 for Phase II, Formulation and Schedule-finding and Table 8, ***Table 9 and Table 10*** for Phase II, Sourcing), a maximum dose interval may be used as presented in Table 19 (Phase I) and Table 20 (Phase II, Formulation and Schedule-finding) and Table 21, ***Table 22 and Table 23*** (Phase II, Sourcing), as applicable.

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

  ** In case of home visits (for Phase II only), the study procedures should be carried out by a qualified person/s as delegated by the Principal Investigator, provided that the compliance with protocol procedures are ensured. Refer to Schedule of Activities for the schedule of visits (see Table 3 and Table 5).

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

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

Table 19 Intervals between study visits/contacts during special circumstances – Phase I

Interval	Length of interval	Allowed interval (Visit window)
Visit V3 → Visit V4	30 days	23 to 51 days (-7 to +21 days)
Visit V3 → Telephone contact T2	120 days	113 to 141 days (-7 to +21 days)
Visit 3 → Telephone contact T3	180 days	173 to 201 days (-7 to +21 days)

Table 20 Intervals between study visits during special circumstances – *Phase II Formulation and Schedule finding*

Interval	Length of interval	Allowed interval (Visit window)
Visit V1 → Visit V2	30 days	23 to 51 days (-7 to +21 days)
Visit V1 → Telephone contact T2	90 days	83 to 111 days (-7 to +21 days)
Visit V2 → Visit V3/TC*	90 days	83 to 111 days (-7 to +21 days)
Visit V3/TC* → Visit V4	60 days	53 to 81 days (-7 to +21 days)
Visit V4 → Visit V5	30 days	23 to 51 days (-7 to +21 days)
Visit V4 → Telephone contact T3	90 days	83 to 111 days (-7 to +21 days)
Visit V4 → Telephone contact T4	180 days	173 to 201 days (-7 to +21 days)
Visit V4 → Telephone contact T5	270 days	263 to 291 days (-7 to +21 days)
Visit V4→Visit V6	360 days	353 to 381 days (-7 to +21 days)

* Visit for C groups (Visit V3) and telephone call for Control group (TC)

Table 21 Intervals between study visits/contacts during special circumstances – Phase II (Sourcing; *0,1 month vaccination schedule*)

Interval	Length of interval	Allowed interval (Visit window)
Visit V2 → Visit V3	30 days	23 to 51 days (-7 to +21 days)
Visit V2 → Telephone contact T1	120 days	113 to 141 days (-7 to +21 days)
Visit V2 → Telephone contact T2	180 days	173 to 201 days (-7 to +21 days)

Table 22 Intervals between study visits/contacts during special circumstances – Phase II (Sourcing; 0,2 month vaccination schedule)

Interval	*Length of interval*	*Allowed interval (Visit window)*
Visit V2 → Visit V3	***15 days***	***8 to 22 days (-7 to +7 days)***
Visit V2 → Visit V4	***30 days***	***25 to 51 days (-5 to +21 days)***
Visit V2 → Telephone contact T2	***120 days***	***113 to 141 days (-7 to +21 days)***
Visit V2 → Telephone contact T3	***180 days***	***173 to 201 days (-7 to +21 days)***

Table 23 Intervals between study visits/contacts during special circumstances – Phase II (Sourcing; 0,6 month vaccination schedule)

Interval	*Length of interval*	*Allowed interval (Visit window)*
Visit V2 → Visit V3	***15 days***	***8 to 22 days (-7 to +7 days)***
Visit V2 → Visit V4	***30 days***	***25 to 51 days (-5 to +21 days)***
Visit V2 → Telephone contact T2	***120 days***	***113 to 141 days (-7 to +21 days)***
Visit V2 → Telephone contact T3	***180 days***	***173 to 201 days (-7 to +21 days)***

8.1. Effectiveness and/or immunogenicity assessments

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

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

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

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

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

8.1.1. Biological samples

8.1.1.1. Blood sample

(Amended 22 March 2022)

Phase I: An overall blood volume of approximately 240 mL per participant will be collected over the course of the Phase I part of the study. An additional 7 mL of blood will be collected at Visit V1 and Visit V2 from all participants for the safety laboratory evaluation. Refer to Table 24 for details.

Table 24 Blood samples at Phase I

Sample type	Quantity	Unit	Timepoint	Subset name/ Group	Day
Blood	Approximately 80	mL	Visit V1 (CCI);	All participants	Day 1
Blood	Approximately 80	mL	Visit V3 (CCI);	All participants	Day 31
Blood	Approximately 80	mL	Visit V4 CCI	All participants	Day 61
Blood	Approximately 7	mL	Visit V1	All participants	Day 1
Blood	Approximately 7	mL	Visit V2	All participants	Day 8

Pre-Vacc, Pre-vaccination timepoint; Post-Vacc, Post-vaccination timepoint

Refer to Table 1 (SoA for Phase I) for details of visits.

Phase II (sourcing): An overall blood volume of approximately 285 mL per participant will be collected over the course of the Phase II, Sourcing part of the study. Please refer to Table 25 and *Table 26* for details.

Table 25 Blood samples at Phase II (Sourcing*; 0,1 month vaccination schedule*)

Sample type	Quantity	Unit	Timepoint	Subset name/ Group	Day
Blood	Approximately 95	mL	Visit V1 (CCI);	All participants	Day 1
Blood	Approximately 95	mL	Visit V2 CCI	All participants	Day 31
Blood	Approximately 95	mL	Visit V3 (CCI	All participants	Day 61

Pre-Vacc, Pre-vaccination timepoint; Post-Vacc, Post-vaccination timepoint
Refer to Table 5 (SoA for Phase II, Sourcing) for details of visits.

Table 26 Blood samples at Phase II (Sourcing; 0,2 and 0,6 month vaccination schedule)

Sample type	*Quantity*	*Unit*	*Timepoint*	*Subset name/ Group*	*Day*
Blood	*Approximately 95*	*mL*	*Visit V1 (CCI);*	*All participants*	*Day 1*
Blood	*Approximately 95*	*mL*	*Visit V3 (CCI);*	C	*Day 76* / *Day 196*
Blood	*Approximately 95*	*mL*	*Visit V4 CCI*		*Day 91* / *Day 211*

Pre-Vacc, Pre-vaccination timepoint; Post-Vacc, Post-vaccination timepoint.
Refer to Table 6 and Table 7(SoA for Phase II, Sourcing) for details of visits.

Note: the total number of participants (healthy adults) planned to be enrolled in the Phase I and Phase II (Sourcing) is required in order to collect sufficient serum samples for the development of assays to be used in the CCI vaccine clinical development program. All participants will be followed for safety up to 6 months after the last vaccination.

Phase II (formulation and schedule-finding): In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA), an overall blood volume of approximately 90mL, per participant, will be collected over the course of the Phase II step of the study. Please refer to Table 27 for details.

Table 27 Blood samples at Phase II (Formulation and schedule-finding)

Sample type	Quantity	Unit	Timepoint	Subset name/ Group	Day
Blood	Approximately 15	mL	Visit V1 (*)	All participants	Day 1
Blood	Approximately 15	mL	Visit V2 (**)	All participants	Day 31
Blood	Approximately 30	mL	Visit V5 (CCI	All participants	Day 211
Blood	Approximately 30	mL	Visit V6 (^)	All participants	Day 541

* Pre-vaccination (Pre-Vacc) for C and Control groups
** Pre-vacc timepoint for C groups. For rest of the groups, C and Control, this is post-vaccination (post-Vacc 1) timepoint
^ Blood sample will be used only for assessment of tertiary objectives
Note: in case of local regulations limiting the amount of blood to be taken in the younger population (e.g 10-12 years of age and/or at the lower bound of the percentile of the growth chart), a reduced amount of blood volume could be drawn at Phase II, Visit 5 and Visit 6. In this population every effort must be done to collect at least 25mL of blood volume, samples will be analysed according to priority ranking provided in Table 29 and Table 30.
Refer to Table 3 (SoA for Phase II, Formulation and Schedule-finding) for details of visits.

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

Note 1: Blood samples are taken from all participants in Phase I and II irrespective of the testing status to maintain the blind of the study. Refer to Section 8.1 for details on how the unused/ left-over samples will be used.

Note 2: Check criteria for blood draw delay as specified in Section 5.5. A topical anaesthetic (e.g. EMLA adhesives or cream) may be used at the site of blood sample draw, according to local practice in order to minimise pain.

8.1.1.2. Urine sample

Urine samples for pregnancy testing will be collected from female participants of childbearing potential prior to the study intervention. Refer to Section 4.1 and 8.2.1.4 for details.

8.1.2. Laboratory assays

(Amended 22 March 2022)

All laboratory testing will be performed at GSK laboratory or in a laboratory designated by GSK. Refer to Section 8.1.1.1 for details on blood sampling.

Effectiveness of the CCI antigens of the CCI vaccine will be evaluated with serum bactericidal assays using endogenous source of human complement (enc-hSBA), on a panel of 110 US representative *N. meningitidis* serogroup B invasive disease strains. Immunogenicity of the vaccine against serogroups A, B, C, W and Y will be evaluated with the serum bactericidal assay using exogenous source of human complement (hSBA). An CCI ***multiplex assay*** will be used to evaluate the serotype-specific IgG responses to A, C, W, and Y.

Table 28 Laboratory assays – Phase I and II

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

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

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

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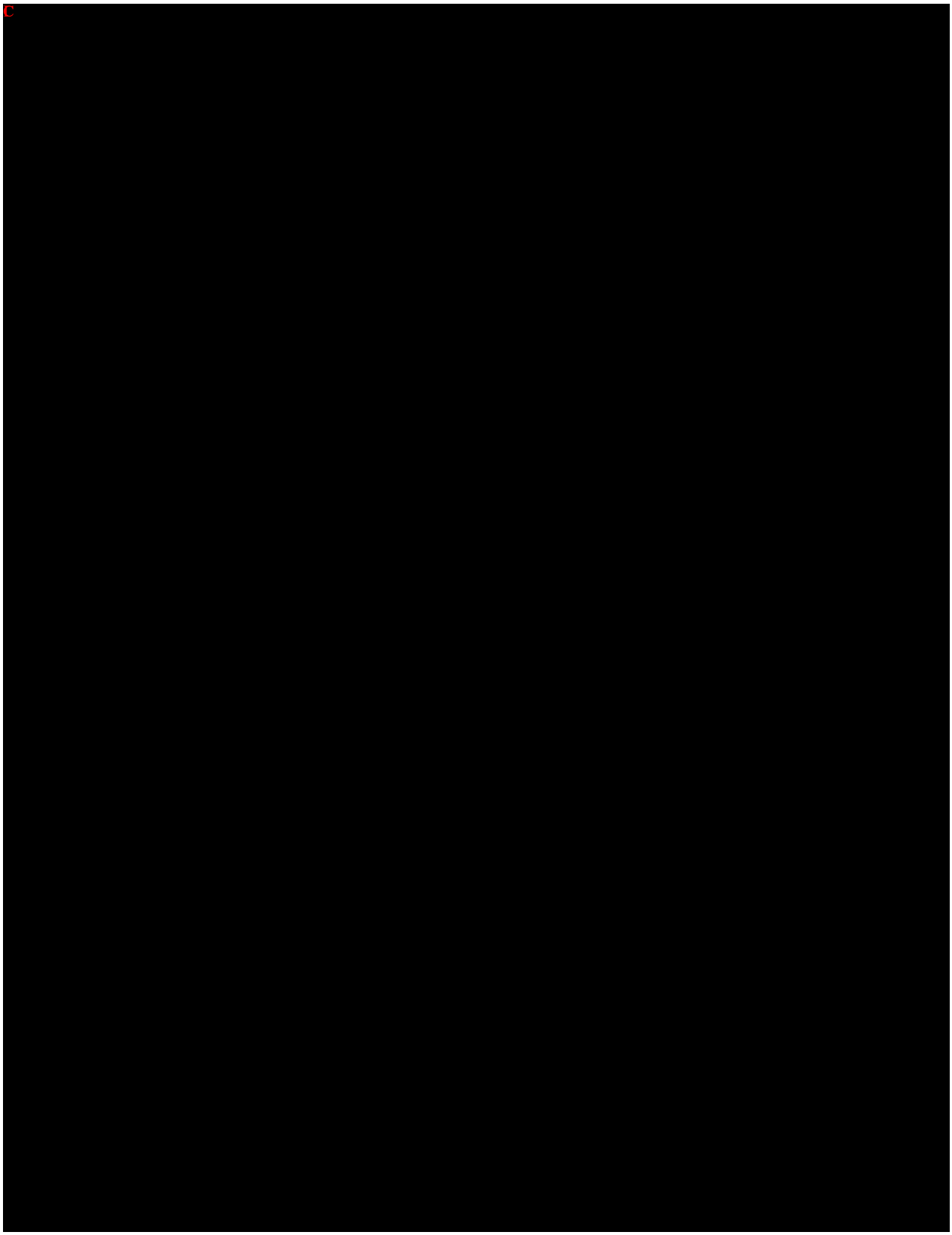


CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

8.1.4. Clinical safety laboratory assessments

Refer to the Section 10.2.1 for the list of clinical laboratory safety assessments required by the protocol. These assessments must be conducted according to the clinical laboratory manual and the SoA.

8.1.5. Immunological correlates of protection

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

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

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

8.2. Safety assessments

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

8.2.1. Pre-vaccination procedures

8.2.1.1. Collection of demographic data

Prior to study enrolment, demographic data will be collected from the participant, including date of birth (Phase I and Phase II (Sourcing): year; Phase II (Formulation and Schedule-finding): month and year), gender, race, ethnicity, weight, and height, and recorded in the participant's eCRF.

For Phase II (Formulation and Schedule-finding) only: At Visit V1 in the Control group, the participant receives 2 injections, one in either arm. Therefore, in order to associate the solicited events reported to the vaccine administered in that arm, the dominant arm (left or right) will be recorded in the eCRF (Table 16).

8.2.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history 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.

8.2.1.3. General and symptom-directed physical examination

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

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

Physical examination at each study visit subsequent to the first study intervention visit, 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.

If the investigator determines that the participant's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled. Treatment of any abnormality observed during this examination should be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.2.1.4. Pregnancy test

Female participants of childbearing potential must perform a urine pregnancy test before the administration of any 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.

Refer to the Section 10.5.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.5. Warnings and precautions to vaccination

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

Refer to the approved product label/package insert of *Bexsero* and *Menveo.*

8.2.2. Study holding rules and safety monitoring

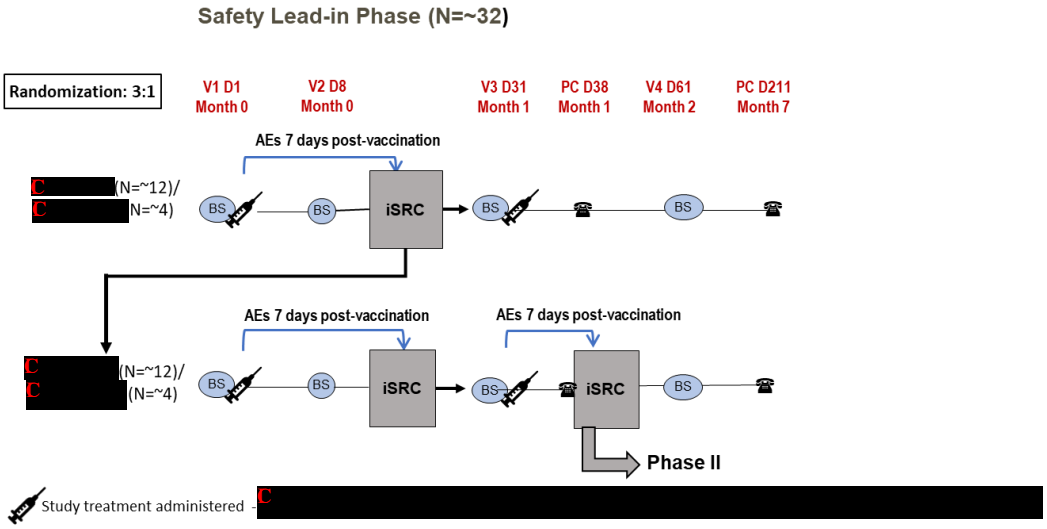
Safety monitoring is specified in the endpoints (Section 9.4) as well as in Table 1 (for Phase I), Table 3 (for Phase II, Formulation and Schedule-finding) and Table 5 (for Phase II, Sourcing).

8.2.2.1. Safety data review

8.2.2.1.1. Safety evaluation

For Phase I of the study, a staggered enrolment of healthy volunteers will be performed, as described in Figure 4.

Figure 4 Step-wise approach for safety review in Phase I (Safety Lead-in)



Abbreviation: N, number of participants; V, clinic visit; D, day; iSRC, internal safety review committee; PC, phone contact; BS, blood sample.
Note: This is a simplified study design aimed to show the safety review in Phase I. To see the detailed study design, refer to Figure 1

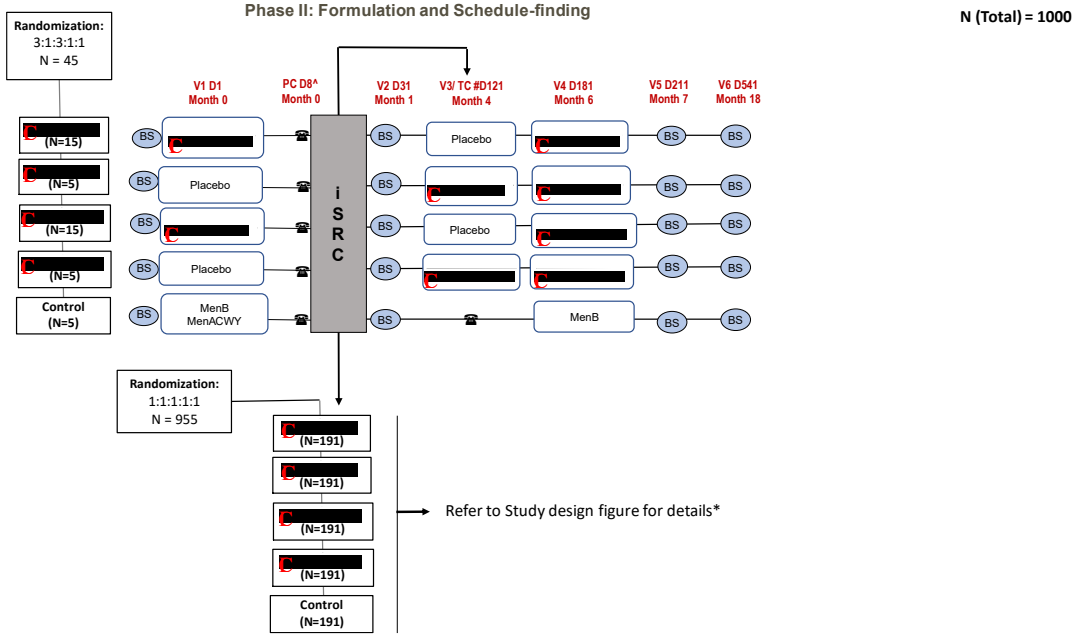
An iSRC, composed of senior GSK experts independent from the study team, will meet at pre-defined timepoints to perform safety monitoring through unblinded review of safety data.

The following step-wise approach will be followed for the safety evaluation during the Phase I Safety Lead-in:

- Step 1: Following the first vaccination in C (12 participants) and C 4 participants) groups, all available safety data from all participants collected up to Day 8 will be evaluated by the iSRC. The iSRC will be responsible for making the first "go-no go" decision based on unblinded data. If a "go" decision is made, the enrolment in groups C will start and the administration of the second vaccination will take place in groups C .
- Step 2: Following the first vaccination in C (12 participants) and C (4 participants) groups, all available safety data from all participants collected up to Day 8 will be evaluated by the iSRC. The iSRC will be responsible for making the second "go-no go" decision based on unblinded data. If a "go" decision is made, the administration of the second vaccination will take place for participants in groups C .
- Step 3: Following the second vaccination in C groups at Day 31, all available safety data from all participants collected up to Day 38 will be evaluated by the iSRC. The iSRC will be responsible for making the third "go-no go" decision based on unblinded data. If a "go" decision is made, the Phase II enrolment will start parallelly for the 2 parts: Phase II (sourcing) and Phase II (formulation and schedule-finding).

For Phase II, Formulation and Schedule-finding part of the study, a staggered enrolment of healthy volunteers will be performed, as described in Figure 5, for the iSRC safety evaluation of the first 45 enrolled participants (Phase II safety lead-in).

Figure 5 Step-wise approach for safety review in Phase II (Formulation and Schedule-finding)



Abbreviation: N, number of participants; V, clinic visit; D, day; TC, Telephone contact for Control group only; iSRC, internal safety review committee; PC, phone contact; BS, blood sample.
^ The phone call at Day 8 is only for the first 45 participants (15 participants in C 5 participants in C , 15 participants in C , 5 participants in C and 5 participants in the Control groups)
# Day 121 Month 4 is a visit for C groups (Visit V3) and is a telephone call for Control group (TC)
Note: This is a simplified study design aimed to show the safety review in Phase II (Formulation and Schedule-finding). To see the detailed study design, refer to Figure 2 (*)

The following step-wise approach will be followed for the safety evaluation during the Phase II (Formulation and Schedule-finding):

- A total of 45 participants will be randomised with 3:1:3:1:1 ratio to the 5 groups (15 in the C , 5 in the C , 15 in the C , 5 in the C and 5 in the Control group). A "go-no go" decision will be taken by the iSRC based on safety and reactogenicity data collected up to Day 8 from these participants (Section 8.2.2.1).
- If the decision is "go", the enrolment in all groups will continue with a randomisation ratio of 1:1:1:1:1 to the target total sample of 1000 participants and the administration of the second vaccination at Month 4 will take place in the 40 participants in C groups (as per study design).

Unblinded safety data to be reviewed by the iSRC include clinical safety laboratory data (only for Phase I), solicited administration site and systemic post-vaccination events, unsolicited AEs, AESIs, and SAEs. Additional safety data may be reviewed and monitored by the iSRC whenever applicable.

Continuous monitoring during the study by the study team will allow for ad-hoc iSRC reviews and/or enrolment hold if any safety concern is identified or a substantial trend emerges outside of the scheduled unblinded safety reviews. Holding rules will be introduced to ensure a well-controlled exposure to the investigational candidate vaccine and to prevent participants from being exposed to any unnecessary safety risks (refer to Section 8.2.2.1.3).

8.2.2.1.2. Outcome of safety evaluation

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

If a safety signal is observed during the safety evaluations or if any of the holding rules 2a-c is met (Table 32), the iSRC Chair (or his/her representative) is responsible for the urgent communication within GSK, including the rationale for the decision to put the study intervention administration on hold or not. Details about the procedures to be followed in case of safety signal or if a holding rule 2 (a-c) is met will be documented in the iSRC Charter.

The Clinical Research & Development Lead (CRDL) who is the primary study contact will inform the local GSK contact. All site staff will be informed about the final decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups by their local GSK contact.

8.2.2.1.3. Study holding rules

Holding rules are defined to ensure well-controlled exposure to the investigational product and they will apply to study participants in the Phase I Safety Lead-in and to the first 45 study participants enrolled in the formulation and schedule-finding Phase II part. The holding rules will hence serve as criteria to point attention to safety signals and require escalation within GSK, in order to decide whether other participants can be exposed. However, medical judgement considering all available safety data at the time of safety review should be the basis for decision to continue the study or not at each step.

The safety holding rules are defined in the Table 32 (Phase I) and Table 33 (Phase II, Formulation and Schedule-finding). If the investigator becomes aware of holding rule 1a-d being met (for Phase I) and holding rule 1a (for Phase II, Formulation and Schedule-finding during the safety lead-in step), he/she will suspend administering the study intervention and will inform GSK immediately (e.g. in case of death or any life-threatening SAEs).

Holding rules 2a-c will be assessed by the iSRC during the safety evaluations on unblinded data.

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

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

The iSRC can also meet ad-hoc during the entire safety lead-in phase (Phase I).

Table 32 Study holding rules – Phase I

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

Abbreviations: AE, adverse event; SAE, serious adverse event.
* Please refer to FDA Toxicology Grading Scale for the definition of the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [FDA, 2007; Refer to Section 10.4, Appendix 4]

Table 33 Study holding rules – Phase II (Formulation and Schedule-finding)

Holding rule	Event	Number or % of participants needed to trigger the hold
1a	Death or any life-threatening **SAE** regardless of causality	≥ 1
2a	Any **Grade 3 solicited administration site event** (lasting 48h or more) in the investigational group, with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 20%
2b	Any **Grade 3 solicited systemic event** (lasting 48h or more) in an investigational group, with an event onset within the 7-day (Day 1-7) post-injection period	≥ 20%
2c	Any **Grade 3 unsolicited AE** in an investigational group, that can be reasonably attributed to the vaccination, with an event onset within the 7-day (Day 1-7) post-injection period	≥ 20%

Abbreviations: AE, adverse event; SAE, serious adverse event;

The investigator is not permitted to begin dosing study participants in subsequent steps (Phase I or Phase II Formulation and Schedule-finding) until the receipt of favourable written documentation of iSRC safety evaluations.

If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention and inform GSK immediately (holding rules 1a-d). Refer to Table 40 for contact information.

The following communication sequence must be followed:

- The concerned site staff must put enrolment and study intervention administration on hold.
- The concerned site staff must immediately inform their local contact defined in the Table 40.
- The LML will inform the other sites of his/her country, LMLs of other countries and the CRDL.
- All informed site staff will send back an email to their local contact to acknowledge receipt of the information.
- GSK Central will further evaluate the case with the iSRC and will take the decision to stop or to restart the vaccination. CRDL who is the primary contact will inform the local GSK contact. All site staff will be informed about that final decision by their local GSK contact.

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

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

(Amended 22 March 2022)

An overview of the protocol-required reporting periods for AEs, SAEs, AESIs and pregnancies is given in Table 34 for Phase I and Table 35 for Phase II. Refer to the Section 10.3.8.1 for details on the time period for recording safety information.

Table 34 Timeframes for collecting and reporting of safety information – Phase I

Event	On V1*	V1 D1***	D7	V3 D31	D37	V4 D61	PC D151	Phase I conclusion D 211 (PC)
Solicited administration site and systemic events								
Unsolicited AEs**								
AEs leading to withdrawal from the study**								
SAEs**								

Event	On V1*	V1 D1***	D7	V3 D31	D37	V4 D61	PC D151	Phase I conclusion D 211 (PC)
SAEs related to study participation or concurrent GSK medication/vaccine								
AESIs**								
Pregnancies**								

* i.e. consent obtained.; V: Visit; D: Day, M: Month; PC=Phone call
** Including COVID-19 infection-related AEs; Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination
*** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration

Table 35 Timeframes for collecting and reporting of safety information – Phase II (Formulation and schedule-finding)

Event	On V1*	V1 D1***	D7	V2 D31	V3# D121	D127	D151	V4 D181	D 187	V5 D 211	PC D361	V6 *Study Conclusion* D541
Solicited administration site and systemic events												
Unsolicited AEs**												
AEs leading to withdrawal from the study**												
SAEs**												
SAEs related to study participation or concurrent GSK medication/vaccine												
AESIs**												
Pregnancies**												

* i.e. consent obtained.; V: Visit; D: Day, M: Month; PC = Phone call

#Solicited AEs and unsolicited AEs will be collected only for C[redacted] groups at Visit V3 (Control group will have a phone call at this time point (TC) where other safety follow-up will be done)

** Including COVID-19 infection-related AEs; Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination

*** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration

Table 36 Timeframes for collecting and reporting of safety information – Phase II (Sourcing; *0,1 month vaccination schedule*)

Event	On V1*	V1		V2		V3	PC	*Study* conclusion
		D1***	D7	D31	D37	D61	Day 151	D 211 (PC)
Solicited administration site and systemic events								
Unsolicited AEs**								
AEs leading to withdrawal from the study**								
SAEs**								
SAEs related to study participation or concurrent GSK medication/vaccine								
AESIs**								
Pregnancies**								

* i.e. consent obtained.; V: Visit; D: Day, M: Month; PC=Phone call
** Including COVID-19 infection-related AEs; Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination)
*** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration

Table 37 Timeframes for collecting and reporting of safety information – Phase II (Sourcing; 0,2 month vaccination schedule)

Event	*On V1**	*V1*		*PC*	*V2*		*V3*	*V4*	*PC*	*Study conclusion*
		*D1****	*D7*	*D31*	*D61*	*D67*	*D76*	*D91*	*Day 181*	*D 241 (PC)*
Solicited administration site and systemic events										
*Unsolicited AEs***										
*AEs leading to withdrawal from the study***										
*SAEs***										
SAEs related to study participation or concurrent GSK medication/vaccine										
*AESIs***										
*Pregnancies***										

** i.e. consent obtained.; V: Visit; D: Day, M: Month; PC=Phone call*

*** Including COVID-19 infection-related AEs; Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination)*

**** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration*

Table 38 Timeframes for collecting and reporting of safety information – Phase II (Sourcing; 0,6 month vaccination schedule)

Event	On V1*	V1 D1***	D7	PC D31	V2 D181	D187	V3 D196	V4 D211	PC Day 301	Study conclusion D 361(PC)
Solicited administration site and systemic events										
Unsolicited AEs**										
AEs leading to withdrawal from the study**										
SAEs**										
SAEs related to study participation or concurrent GSK medication/vaccine										
AESIs**										
Pregnancies**										

** i.e. consent obtained.; V: Visit; D: Day, M: Month; PC=Phone call*
*** Including COVID-19 infection-related AEs; Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination)*
**** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration*

The investigator or designee will record and immediately report all SAEs to the sponsor via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 34. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention, the

investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 40.

8.3.2. Method of detecting AEs and SAEs, pregnancies and other events

Detection and recording of AE/SAE/AESI/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

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

8.3.2.1. Clinically significant abnormal laboratory findings (Phase I)

The investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All clinically significant abnormal laboratory test values reported for participants in Phase I at Visit V1 and Visit V2 should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator or LML. Refer to the Section 10.3.6 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the aetiology of the abnormal value should be identified and the sponsor notified.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/AESI/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 39. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of Suspected Unexpected Serious Adverse Reactions (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/regulatory agencies

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

Please refer to the Section 10.3.10 for further details regarding the reporting of SAEs/AESIs/pregnancies.

Table 39 Timeframes for submitting SAE, pregnancy and other events reports to GSK

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

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

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

Table 40 Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

Study contact for questions regarding SAEs, AESIs, pregnancies Refer to the local study contact information document	**Study contact for reporting of study holding rules** As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the LML.
Back up study contact for reporting SAEs, AESIs, pregnancies Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com US sites only: Fax: 1 610 787 7053	**Back up study contact for escalation of holding rules** If applicable, refer to the local study contact information document.

8.3.4. Treatment of adverse events

Any medication administered for the treatment of an SAE/AESI should be recorded in the eCRF (refer to the Section 10.3.10.1).

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

8.3.6. Medical device deficiencies

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

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

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

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.7 for definitions and details on recording and reporting of these events.

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

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

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

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to section 10.7.3 for details of reporting.

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

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics and/or Pharmacogenomics

Not applicable.

8.6. Biomarkers

Not applicable.

8.7. Immunogenicity

Refer to Section 8.1.

8.8. Health outcomes

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

9.1.1. Phase I (Safety Lead-in) and Phase II (Sourcing)

There is no hypothesis for Phase I.

9.1.2. Phase II (Formulation and Schedule-finding)

9.1.2.1. Superiority of vaccine effectiveness of the CCI vaccine C) when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenB)

For demonstration of superiority of the Vaccine effectiveness (VE), defined as the percentage of samples with bactericidal serum activity at 1:4 dilution using enc-hSBA against a panel of 110 randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains, of CCI vaccine compared to Control vaccine (MenB) the following hypothesis will be tested:

Null hypothesis:

H0: π CCI ***– π Control ≤ 5%***
vs.

Alternative hypothesis:

H1: π CCI ***– π Control > 5%***

Where: π CCI and π Control represent the percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains at 1 month after the last vaccination in the ABCWY groups and in the Control group and 5% is the superiority margin for the difference in percentages of samples with bactericidal serum activity between ABCWY and Control groups. Superiority of CCI to Control vaccine (MenB) will be demonstrated if the Lower Limit (LL) of the 2-sided 97.5% Confidence Interval (CI) for the group difference in percentages of samples with bactericidal serum activity against a randomly selected panel is above 5%.

9.1.2.2. Immunological non-inferiority of CCI vaccine CCI when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenACWY)

For demonstration of non-inferiority of CCI vaccine versus Control vaccine (MenACWY – in participants without a previous MenACWY vaccination (unprimed)), the following non-inferiority hypotheses will be tested simultaneously for each of the 4 serogroups A, C, W, and Y:

Null hypothesis:

H0: π CCI – π Control ≤ -10%
vs.

Alternative hypothesis:

H1: π CCI – π Control > -10%

Where: π CCI represents the percentages of participants with a 4-fold rise 1 month after the last vaccination in the groups receiving CCI and π Control represents the percentages of participants with a 4-fold rise 1 month after the first vaccination in the Control group (participants receiving MenACWY without a previous MenACWY vaccination (unprimed)); and -10% is the non-inferiority margin for the difference in 4-fold rise between groups receiving CCI and Control group. Immunological non-inferiority of CCI vaccine to Control (MenACWY) will be demonstrated if the LL of the 2-sided 97.5% CI for the group difference in percentages of participants achieving a 4-fold rise in hSBA titres is above -10% for each serogroup.

9.2. Sample size determination

Participants who withdraw from the study will not be replaced.

9.2.1. Phase I (Safety Lead-in)

Thirty-two (32) participants are to be enrolled in the 4 arms of Phase I of the study; 12 each in the C groups and 4 each in the C groups.

9.2.2. Phase II (Formulation and Schedule-finding)

A thousand (1000) participants are to be enrolled in 5 arms of Phase II of the study, 206 participants for both C arms and 196 participants for C and Control arms. C

[redacted]

C [redacted]

The formulation and schedule for future clinical development of the CCI vaccine will be selected taking also into considerations the results of the Phase II secondary endpoints, following the success of the primary objectives.

9.2.3. Phase II (Sourcing)

(Amended 22 March 2022)

One hundred and seven (107) participants ***have been*** enrolled in 2 arms of Phase II (Sourcing) of the study, in group (1:1 randomisation). ***At the time of this amendment (Protocol amendment 4) enrolment to these groups was stopped.***

Two hundred and forty (240) participants are to be enrolled in 4 arms, 60 participants each in groups (1:1:1:1 randomization).

CCI

9.3.1. Criteria for elimination from analysis

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

9.4. Statistical analyses

9.4.1. Primary endpoint(s) – Phase I (Safety Lead-in)

Primary Endpoint	Statistical Analysis Methods
Safety	CCI [redacted]

Primary Endpoint	Statistical Analysis Methods
	CCI [redacted]

9.4.2. Primary endpoint(s) – Phase II (Formulation and Schedule-finding)

(Amended 22 March 2022)

Primary Endpoint	Statistical Analysis Methods
Superiority of effectiveness	CCI [redacted]
Immunological non-inferiority	
Safety	

Primary Endpoint	Statistical Analysis Methods
	CCI [redacted]

9.4.3. Primary endpoint(s) – Phase II (Sourcing)

(Amended 22 March 2022)

Primary Endpoint	Statistical Analysis Methods
Safety	CCI [redacted]
[redacted]	[redacted]

Primary Endpoint	Statistical Analysis Methods
	CCI [redacted]

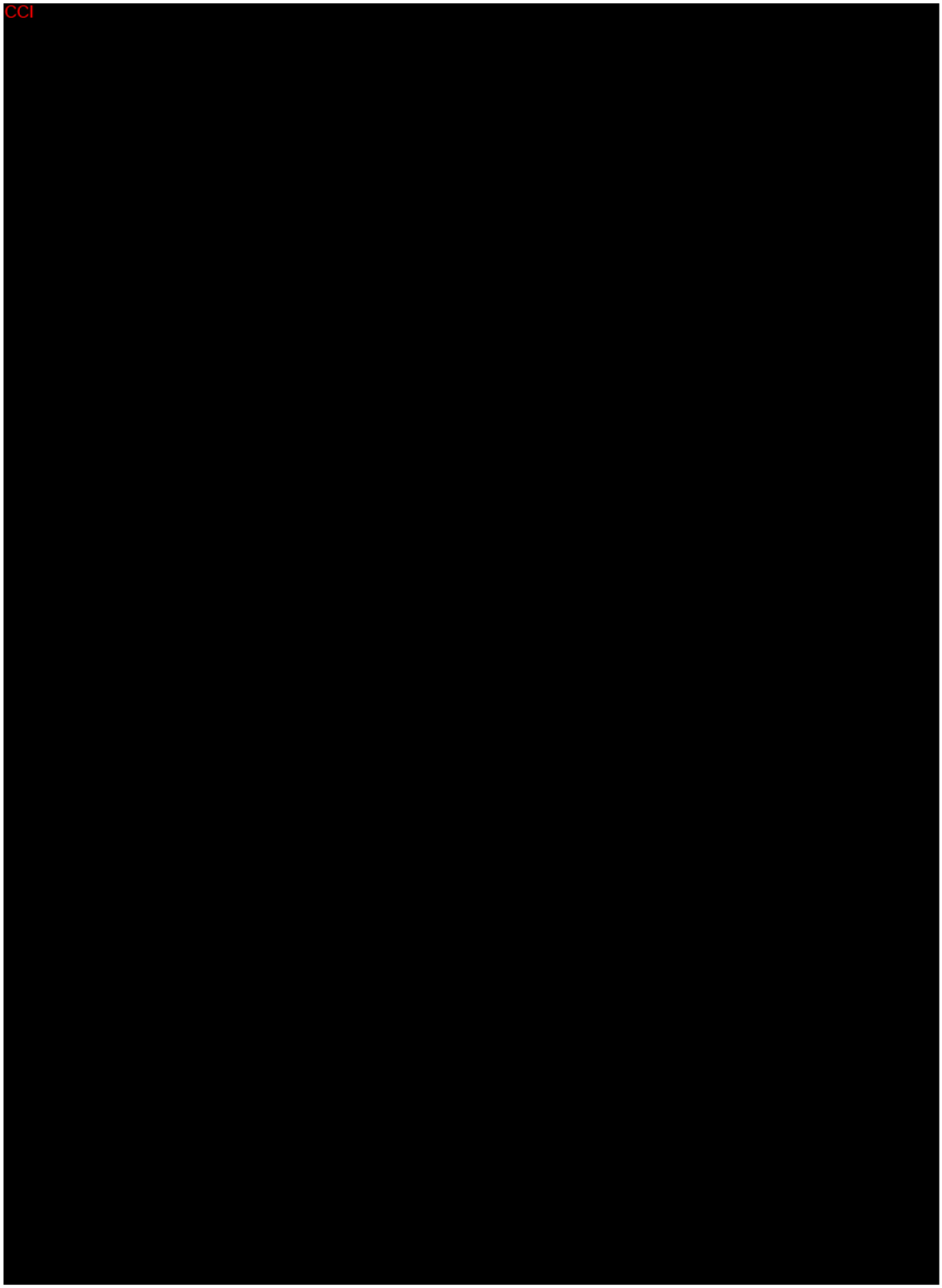
9.4.4. Secondary endpoint(s) – Phase II (Formulation and Schedule-finding)

Secondary Endpoint	Statistical Analysis Methods
Description of the distribution of B strains killed	CCI [redacted]
Immune response to serogroup B indicator strains	[redacted]

Secondary Endpoint	Statistical Analysis Methods
Immune response to serogroups A,C,W and Y	CCI [redacted]

9.4.5. Tertiary endpoint(s) – Phase II (Formulation and Schedule-finding)

CCI



C

CCI

CCI

[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and ethical considerations

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

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

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

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

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

Freely given and written/witnessed/thumb printed informed consent must be obtained from each participant and/or each participant's parent(s)/LAR(s)/witness (per phase: Phase I, Phase II, Sourcing or Phase II, Formulation and Schedule-finding) and participant informed assent (for Phase II, Formulation and Schedule-finding), as appropriate, prior to participation in the study.

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

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

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

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

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

Phase II (Formulation and Schedule-finding): Re-consent must be obtained in accordance with local laws and regulations for participants who become legally emancipated during the study, i.e. reach the legal age of consent. The participant can provide consent by signing/witnessing/thumb printing an ICF, similar to that provided to the parent(s)/LAR(s) at study start, which summarises the study and includes a consent statement and documents that the participant agrees to continue participating in the study.

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

10.1.4. Data protection

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

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

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

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

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

10.1.5. Committees structure

10.1.5.1. Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 [ICH, 1997]. A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical

Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

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

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

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

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

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

iii. to the regulatory authority(ies).

10.1.5.2. internal Safety Review Committee

Refer to Section 8.2.2 for details.

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 Clinical 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 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

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

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

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

GSK intends to make anonymised patient-level data from this trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

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

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

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

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

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

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

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

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

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

10.1.8. Source documents

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

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

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

10.1.9. Study and site start and closure

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

Regular closure of study sites will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

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

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

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

10.1.9.1. Study conclusion

(Amended 22 March 2022)

At Phase I conclusion phone call (Day 211), Phase II (Formulation and Schedule-finding) conclusion visit (study conclusion; Visit 6, Day 541) and Phase II (Sourcing) conclusions phone call (Day 211 ***in*** C ***groups, Day 241 in*** C ***groups and Day 361 in*** C ***groups***), the investigator will:

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

10.1.10. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Protocol-required safety laboratory assessments

Haematology and biochemistry assays for safety assessment will be performed in all participants in Phase I, in the investigator's laboratory using standard procedures as per local practice (refer to Table 44 and Table 1).

Table 44 Haematology and biochemistry tests – Phase I

System	Discipline	Component	Method	Scale	Laboratory
Whole blood	Haematology	Leukocytes (White Blood Cells)	Per contract laboratory's procedures	Quantitative	Investigator's institution/laboratory
		Neutrophils*	Per contract laboratory's procedures	Quantitative	
		Lymphocytes*	Per contract laboratory's procedures	Quantitative	
		Basophils*	Per contract laboratory's procedures	Quantitative	
		Monocytes*	Per contract laboratory's procedures	Quantitative	
		Eosinophils*	Per contract laboratory's procedures	Quantitative	
		Haemoglobin	Per contract laboratory's procedures	Quantitative	
		Platelets	Per contract laboratory's procedures	Quantitative	
		Erythrocytes (Red Blood Cells)	Per contract laboratory's procedures	Quantitative	
Serum	Biochemistry	Alanine Aminotransferase (ALT)	Per contract laboratory's procedures	Quantitative	Investigator's institution/laboratory
		Aspartate Aminotransferase (AST)	Per contract laboratory's procedures	Quantitative	
		Creatinine	Per contract laboratory's procedures	Quantitative	

* For White Blood Cell (WBC) differential count.

The tests detailed in Table 44 will be performed by the local laboratory.

10.2.2. Effectiveness and immunogenicity laboratory assessments

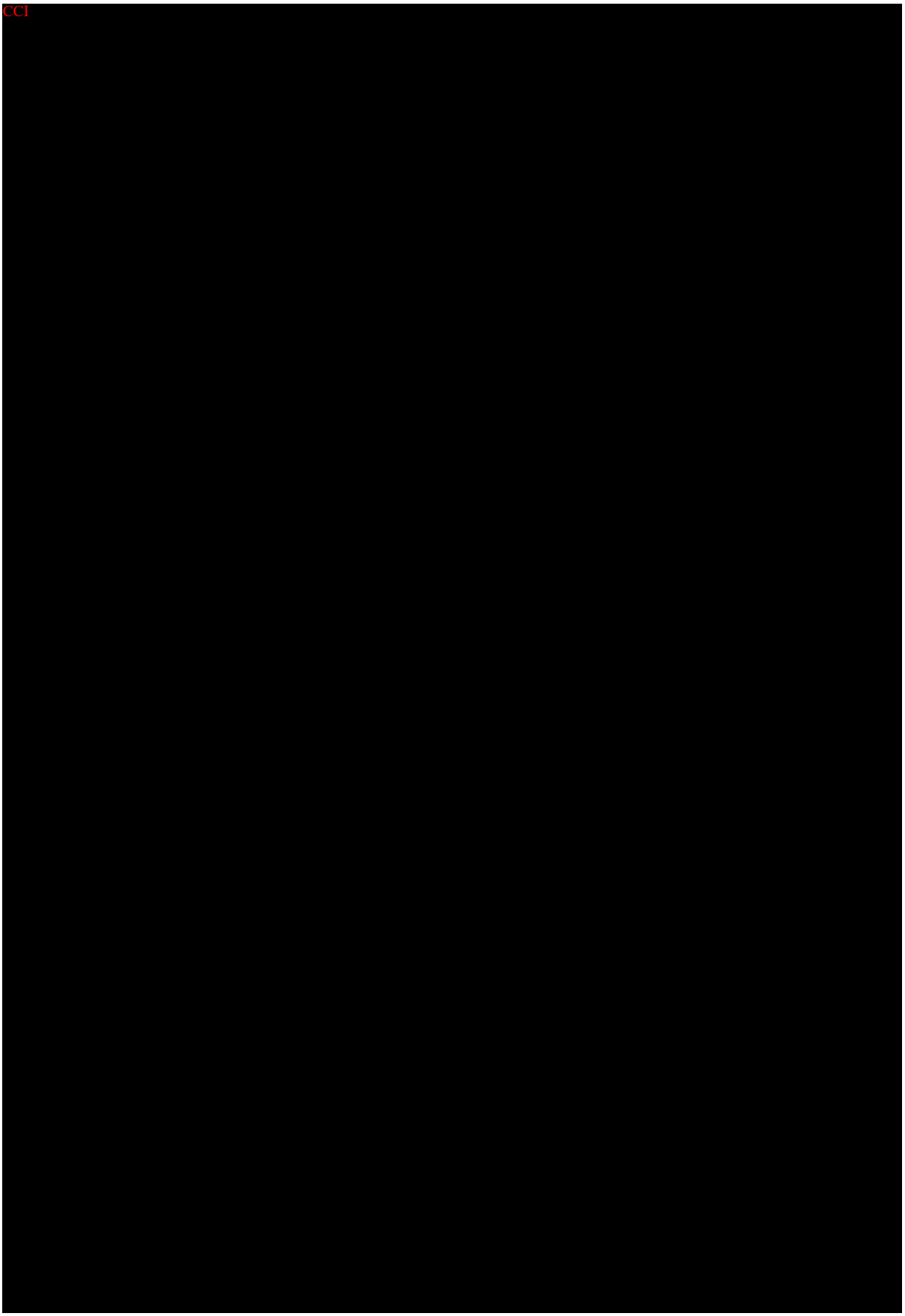
The tests detailed in Table 28 will be performed at GSK or at a laboratory designated by GSK where the assays are available for the intended use.

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

A urine pregnancy test will be conducted as needed for women of childbearing potential (refer to Section 8.1.1.2).

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

CCI



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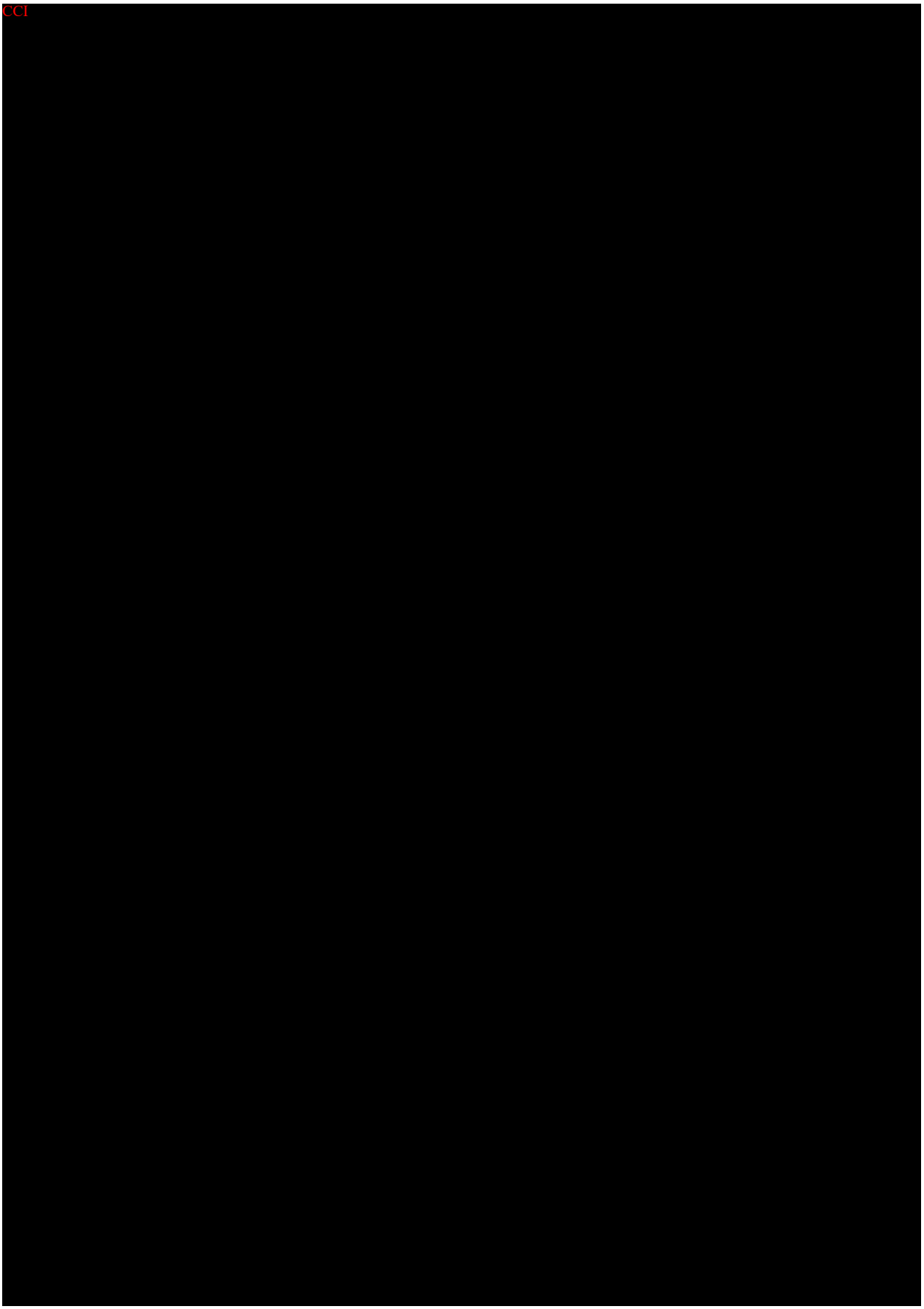


10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting Definition of AE

10.3.1. Definition of an Adverse Event (AE)

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

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits).
- Significant failure of an expected pharmacologic or biological action.
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT Meeting the AE Definition
• Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Pre-existing conditions or signs and/or symptoms present in a participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF. • Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:	
a.	Results in death
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c.	Requires hospitalisation or prolongation of existing hospitalisation Note: In general, hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. The event will also be considered serious if a complication prolongs hospitalisation or fulfils any other serious criteria. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.
d.	Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e.	Is a congenital anomaly/birth defect in the offspring of a study participant

f.	Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g.	Other situations Medical or scientific judgement must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalisation.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 45 Solicited administration site events – Phase I and II

All age groups
Injection site Pain
Erythema
Swelling
Induration

b. Solicited systemic events

The following systemic events will be solicited:

Table 46 Solicited systemic events – Phase I and II

All age groups
fever [body temperature ≥ 38.0°C]
nausea
fatigue
myalgia
arthralgia
headache

Note: participants/participants' parent(s)/LAR(s) will be instructed to measure and record the oral* 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.

* Preferred location for measuring temperature will be the oral cavity. In case the participant/ participant's parent(s)/LAR(s) use any other route for measuring temperature, this needs to be recorded in the eDiary.

10.3.4. Unsolicited adverse events

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

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or an emergency room visit, or visit to/by a health care provider). The 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/parental/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant/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. Adverse events of special interest (AESIs)

Adverse events of special interest are pre-defined (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 characterise and understand it.

10.3.5.1. Potential immune-mediated diseases (pIMDs)

Potential immune-mediated diseases (pIMDs) are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 47.

The investigator must exercise his/her medical/scientific judgement to determine whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

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

Table 47 List of potential immune-mediated diseases (pIMDs)

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

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

10.3.5.2. Other adverse events of special interest

10.3.5.2.1. Arthritis

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

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

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

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

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.

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

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

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

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to the Section 10.3.2 for definition of SAE.

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

(Amended 22 March 2022)

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

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

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

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

An Electronic Diary (eDiary), hereafter referred to as Participant Diary, will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete the Participant Diary.

Anyone who measures administration site or systemic events and who will record the event in the Participant Diary should be trained on using the Diary. This training must be documented in the participant's source record. If any individual other than the participant/participant's parent(s)/LAR(s) is making entries in the Participant Diary, their identity must be documented in the Participant Diary/participant's source record.

Note (Phase II, Formulation and Schedule-finding part only): eDiaries may be filled in by a minor participant 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 the 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).

- Verify completed eDiaries during discussions with the participant/participant's parent(s)/LAR(s) on:
  - Visit *V*3 (Day 31) and Visit *V*4 (Day 61) – Phase I

- Visit *V*2 (Day 31), Visit *V*4 (Day 181) and Visit *V*5 (Day 211) – Phase II, Formulation and Schedule finding, C groups
- Visit *V*2 (Day 31) and Visit *V*5 (Day 211) – Phase II, Formulation and Schedule finding, Control group
- Visit *V*2 (Day 31) and Visit *V*3 (Day 61) – Phase II, Sourcing, C ***groups.***
- ***Phone call (T1, Day 31), Visit V3 (Day 76) and Visit 4 (Day 91) – Phase II, Sourcing,*** C ***groups.***
- ***Phone call (T1, Day 31), Visit V3 (Day 196) and Visit 4 (Day 211) - Phase II, Sourcing,*** C ***groups.***

Collect eDiaries on Visit 4 (Day 61) for Phase I participants, Visit 5 (Day 211) for Phase II (Formulation and Schedule-finding) participants and Visit 3***/4*** (***V3,*** Day 61 ***for*** C ***groups, V4, Day 91 for*** C ***groups and V4, Day 211 in*** C ***groups***) for Phase II (Sourcing) participants.

Note (Phase II, Formulation and Schedule-finding only): If the eDiary has been filled in by a minor participant, the investigator or delegate should verify the reported information during a discussion with the minor participant preferably in the presence of his/her parent(s)/LAR(s).

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

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

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

10.3.8.1. Time period for collecting and recording AEs, SAEs, AESIs and pregnancies

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

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

Solicited events that are ongoing after the 7-day reporting period may continue to be recorded in the eDiary until resolution or up to 30 days post-vaccination (ie, recording period for unsolicited AEs) whichever occurs first and do not need to be entered as an AE

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

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

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

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

Refer to Table 34, Table 35 and Table 36 for the time period for collecting and recording unsolicited AEs, SAEs, AESIs and pregnancies.

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

After the initial AE/SAE/AESI/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in the Section 10.3.5), will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

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

10.3.8.2.1. Follow-up during the study

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

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

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

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE/AESI using an electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange

for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE/AESI as fully as possible.

10.3.8.2.3. 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 Expedited AEs 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.

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, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND it is considered by the investigator to be reasonably related to the study intervention, he/she must report this information to GSK as described in the Section 10.3.10.

10.3.8.3. 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 faxed to the Study contact for reporting SAEs (refer to the Section 8.3.3.1) or to GSK VCSP department within the defined reporting time frames specified in the Table 39.

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

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

Table 48 Intensity scales for solicited events in adults and children of 10 years of age or more

Adults/Child (≥10 years)		
Event	**Intensity grade**	**Parameter**
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Erythema at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
Induration at administration site		Greatest surface diameter in mm
Temperature*		Temperature in °C/°F (with 1 decimal)
Nausea	0	Normal

Adults/Child (≥10 years)		
Event	**Intensity grade**	**Parameter**
	1	Mild: Nausea that is easily tolerated
	2	Moderate: Nausea that interferes with normal activity
	3	Severe: Nausea that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity

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

The maximum intensity of local injection Site Induration, Swelling, Erythema will be scored at GSK as follows:

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

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

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

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

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

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

such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

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

10.3.9.2. Assessment of causality

All solicited administration site and systemic events will be considered causally related to administration of the study intervention. The complete list of these events is provided in Table 45 and Table 46.

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

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB and/or SmPC and/or Prescribing Information for marketed products to assist in making his/her assessment.

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

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

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

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

Possible contributing factors include:

- Medical history.
- Other medication.

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

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

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

10.3.9.3. Medically attended visits

(Amended 22 March 2022)

For each solicited and unsolicited AE the participant experiences (Refer to Table 34, Table 35, Table 36, ***Table 37 and Table 38***), the participant/participant's parent(s)/LAR(s) will be asked if he/she/the participant received medical attention (defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the eDiary/ eCRF.

10.3.9.4. Assessment of outcomes

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

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

10.3.9.5. Recording of AEs related to COVID-19

(Amended 22 March 2022)

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

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

Note: Due to the rapid evolution of the COVID-19 pandemic situation, it is important to adhere to the most recent guidelines released by WHO. Please refer to the WHO website for the latest guidance.

10.3.9.5.1. WHO Case Definition

- Suspected COVID-19 case

  A. A person who meets the clinical AND epidemiological criteria

  Clinical criteria:

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

  AND

  Epidemiological criteria:

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

  OR

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

- Probable COVID-19 case

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

  OR

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

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

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

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

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

OR

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

OR

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

- Confirmed COVID-19 case ***[WHO, 2020]***

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

10.3.10. Reporting of SAEs, AESIs, pregnancies and other events

10.3.10.1. Events requiring expedited reporting to GSK

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

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

Refer to the Table 39 for the details on timeframes for reporting of SAEs/ AESIs/ pregnancies.

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

Fax transmission is the preferred method of forwarding the paper Expedited AEs Report to the study contact for reporting SAEs (refer to the Table 40). In the absence/dysfunction of fax equipment, the study contact for reporting SAEs must be notified by telephone within 24 hours. As soon as the fax equipment is working again, the investigator (or designee) must fax the report to the study contact for reporting SAEs, within 24 hours.

Refer to the Section 10.3.10.2 for information on back up systems in case the electronic reporting system does not work.

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

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

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

10.4. Appendix 4: FDA's toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials applied for this study

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Table 49 Laboratory abnormalities

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)**
Serum*				
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN***	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Haematology*				
Haemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Haemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Haemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Haemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterisation of the laboratory abnormalities as Potentially Life-Threatening (Grade 4).
***ULN is the upper limit of the normal range.

10.5. Appendix 5: Contraceptive guidance and collection of pregnancy information

10.5.1. Definitions

(Amended 22 March 2022)

10.5.1.1. Woman of Childbearing Potential (WOCBP)

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

10.5.1.1.1. Women not considered as women of childbearing potential

- **Premenarchal**

  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.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- **Premenopausal female with ONE of the following:**
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - ***Current bilateral tubal ligation or occlusion***

Note: Documentation can come from the site personnel's: review of 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, a single FSH measurement is insufficient.

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

10.5.2. 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 50).

Table 50 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent [a] ***Failure rate of <1% per year when used consistently and correctly***
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable • oral
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomised partner *(A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilisation prior to the female participant's entry into the study, and this male is the sole partner for that participant, *(The information on the male sterility can come from the 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 study and the preferred and usual lifestyle of the participant.)*

[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

10.5.3. Collection of pregnancy information

10.5.3.1. Female participants who become pregnant

Refer to the Sections 8.3.1, 8.3.2, 10.3.8.1 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will discontinue study intervention or be withdrawn from the study.

10.6. Appendix 6: Genetics

Not applicable.

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

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

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.

- An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:

  – insufficient or inadequate instructions for use (i.e. user error), or

  – any malfunction of a medical device, or

  – intentional misuse of the medical device.

10.7.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

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

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

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- E-mail/Facsimile transmission of the paper 'Medical device or combination product with device deficiency/incident report form' is the preferred method to transmit this information to the sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of 'Medical device or combination product with device deficiency/incident report form' sent by overnight mail or courier service.
- Contacts for reporting can be found in Section 8.3.3.1.
- GSK will review all device deficiencies, determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.8. Appendix 8: Country-specific requirements

Not applicable.

10.9. Appendix 9: Abbreviations and glossary of terms

10.9.1. List of abbreviations

ADE:	Adverse Device Effect
AE:	Adverse Event
AESI:	Adverse event of special interest
ANOVA:	Analysis of variance
BMI:	Body mass index
CLS:	Clinical Laboratory Sciences
COVID-19:	Coronavirus disease-2019
CRDL:	Clinical Research & Development Lead
CRM_{197}:	*Corynebacterium diphtheriae* Cross Reacting Material-197
CSR:	Clinical Study Report
eCRF:	electronic Case Report Form
eDiary:	Electronic Diary
Enc-hSBA:	Endogenous Complement Human Serum Bactericidal Assay
EoS:	End of Study
EU:	European Union
fHbp:	factor H binding protein
FTIH:	First-time in human
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMR:	Geometric Mean Ratio
GSK:	GlaxoSmithKline Biologicals SA
HCP:	Qualified study staff/healthcare professionals
hSBA:	Human Serum Bactericidal Assay
IAF:	Informed Assent Form
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation

IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IMD:	Invasive Meningococcal Disease
IRB:	Institutional Review Board
iSRC:	Internal Safety Review Committee
LAR:	Legally Acceptable Representative
LLOQ:	Lower limit of quantitation
LML	Local Medical lead
LOD:	Limit of detection
LSLV:	Last Participant Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
N. meningitidis:	*Neisseria meningitidis*
NadA:	Neisseria Adhesin A
NHBA:	Neisserial Heparin Binding Antigen
pIMD:	Potential Immune-Mediated Disease
PorA:	Porin A
QTL	Quality Tolerance Limit
SADE:	Serious Adverse Device Effect
SAE:	Serious Adverse Event
SBIR:	Source data Base for Internet Randomisation
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
US:	United States
USADE	Unanticipated Serious Adverse Device Effect
VE:	Vaccine effectiveness
WHO:	World Health Organization
WOCBP	Woman of Childbearing Potential

10.9.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the trial 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 trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. **For Phase I and Phase II Sourcing:** In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. **For Phase II Formulation and Schedule-finding:** Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or

	living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Combination product	Combination product comprises any combination of • drug • device • biological product Each drug, device and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled participant	'Enrolled' means a participant's/parent's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 of the protocol for the definition of 'enrolled set' applicable to the study.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.

Investigational vaccine:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions.
Legally acceptable representative	An individual, judicial or other body authorised under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical trial. The terms legal representative or legally authorised representative are used in some settings.
Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.
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 number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Remote visit:	Refers to the visit conducted in the place other than the study site.
Randomisation:	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical trial).

Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Sub-cohort:	A group of participants for whom specific study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g. ages, vaccination schedule, etc.) at the time of enrolment.
Telemedicine:	Telemedicine refers to the use of information technologies and electronic communications to provide clinical services to patients virtually. The digital transmission of medical imaging, virtual medical diagnosis and evaluations, and video consultations with specialists are all examples of telemedicine.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Virtual visit:	Refers to study visits conducted using multimedia or technological platforms.

10.10. Appendix 10: Protocol Amendment history

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

DOCUMENT HISTORY	
Document	Date of Issue
Protocol Amendment 4	22 March 2022
Protocol Amendment 3	29 September 2021
Protocol Amendment 2	21 June 2021
Protocol Amendment 1	7 May 2021
Original Protocol	11 January 2021

Amendments summary of changes table:

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol Amendment 1	7 May 2021	Section 1.3, Schedule of activities Section 8.1.1.1, Biological samples	The blood volume for safety assessment needs to change to approximately 7 mL from approximately 6 mL.	In order to avoid collecting lower volume of blood, it was determined that the blood sample tubes should be filled to capacity.
Protocol Amendment 2	21 June 2021	Section 2.3, Benefit/Risk assessment Section 4.1.2.1, Phase II formulation and schedule-finding Section 4.2, Scientific rationale for study design Section 5.1, Inclusion criteria Section 6.1, Study intervention(s) administered (Table 12) Section 8.2.1.5, Warnings and precautions to vaccination Section 8.2.21, Safety data review	The Tdap vaccine (*Boostrix*) has been removed from the study design of Phase II Formulation and schedule-finding. It has been replaced by placebo as applicable.	To avoid potential confounding factors that might impact selection of dosage and schedule for further development which is one of the primary aims of the study.
		Section 4.1.2.1, Phase II formulation and schedule-finding Section 6.3.5, Blinding and unblinding	The blinding for Phase II formulation and schedule-finding has been changed to 'partially-blind' from 'observer-blind' (ABCWY groups = observer-blind; Control group = open-label). The section on Blinding has been updated accordingly. Note: The blinding has been removed from the study title as it differs between the phases in the study.	Since Tdap vaccine has been removed, the 4 groups administering CCI vaccine in different dosages and schedules are observer-blind; however the Control group receiving MenACWY and MenB vaccines at Visit V1 will be open-label.
Protocol Amendment 2	21 June 2021	Section 4.1.2.1, Phase II: Formulation and Schedule-finding Section 8.2.2.1, Safety data review: Section 9.2, Sample size determination, 9.2.2, Phase II (Formulation and Schedule-finding) Section 9.2.2.1, Superiority of vaccine effectiveness of the CCI	The number of participants in Phase II Formulation and Schedule-finding has been increased to 1000 from 885 (45 in Step 1 and 955 in Step 2).	Due to the split in the alpha (for parallel testing of CCI dose), the sample size has been increased to maintain the power of the analysis.

Document	Date of issue	Section # and title	Description of change	Brief rationale
		vaccine CCI) when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenB) Section 9.2.2.2, Immunological non-inferiority of CCI vaccine CCI when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenACWY)		
Protocol Amendment 2	21 June 2021	Section 4.1.2.2, Phase II Sourcing Section 9.2.3, Phase II (Sourcing)	The number of participants in Phase II sourcing have been increased to 226 from 126 earlier.	To support the assay development.
		Section 6.1, Study intervention(s) administered Section 8.3.6, Medical device deficiencies Section 10.7: Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)	Product category included Implementation of wording on medical device deficiency for combination products for Post Marketing Safety Reporting.	In line with the FDA Combination Product Post Marketing Safety Reporting guidance.
		Section 1.3, Schedule of activities Section 10.3.8.1, Time period for collecting and recording AEs, SAEs, AESIs and pregnancies	Details on post-injection assessment have been added.	To clarify on the data to be collected during the post-injection assessment period.
		Section 3, Objectives and endpoints (Table 7) Section 8.1.2, Laboratory assays Section 8.1.3, Immunological read-outs Section 10.2.2.2.1, MenB serum bactericidal assays – CCI and *Bexsero*	CCI	
		Section 8.3.3, Regulatory reporting requirements for SAEs, pregnancies and other events	The timeframe for submitting pregnancy report to GSK is now 24 hours (changed from 2 weeks).	Changed in line with the pregnancy reporting guidelines for Vaccine studies.
		Section 2.3, Benefit/Risk assessment	The Tdap vaccine (Boostrix) has been removed from the study design of Phase II	To avoid potential confounding factors that might impact selection of dosage and

Document	Date of issue	Section # and title	Description of change	Brief rationale
		Section 4.1.2.1, Phase II formulation and schedule-finding Section 4.2, Scientific rationale for study design Section 5.1, Inclusion criteria Section 6.1, Study intervention(s) administered (Table 12) Section 8.2.1.5, Warnings and precautions to vaccination Section 8.2.21, Safety data review	Formulation and schedule-finding. It has been replaced by placebo as applicable.	schedule for further development which is one of the primary aims of the study.
Protocol Amendment 3	29 September 2021	Section 1.3 Schedule of activities, Table 3 Section 1.3 Schedule of activities, Table 4 Section 2.3 Benefit/Risk assessment Section 3 Objectives and endpoints, Table 7 Section 4.1.2.1 Phase II: Formulation and Schedule-finding Section 6.1 Study intervention(s) administered, Table 12 Section 8 Study assessments and procedures, Table 16 Section 8.2.2.1.1 Safety evaluation Section 8.3.1 Time period and frequency for collecting AE, SAE and other safety information, Table 28 Section 10.3.8 Recording and follow-up of AEs, SAEs, AESIs and pregnancies	In the Phase II Formulation and Schedule finding, the participants in the Control group will have no study intervention at Visit V3 (Month 4). This visit (Visit V3) has been replaced by a phone call (TC). Applicable changes made in all sections noted here. Refer to Section 10.10.1 for details.	Since the Control group is open-label, administration of placebo at Visit V3 (Month 4) is not required. Therefore this group will not have any study intervention administered at this timepoint. This visit has been replaced by a phone call.
		Section 1.3 Schedule of activities, Table 1, Table 3, Table 5 Section 8.1.1.1 Blood sample	The word 'approximately' added when referring to overall volume	To align with the fact that individual volumes are presented as 'approximately xx mL', this word has been added to the overall blood volume as well.
		Section 8.3.1 Time period and frequency for collecting AE, SAE and other safety information, Table 27, Table 28, Table 29	Footnote added to clarify the follow-up for unsolicited AEs post-vaccination	Since the way the shading of the table is done may lead to misinterpretation regarding

Document	Date of issue	Section # and title	Description of change	Brief rationale
				the follow-up period for unsolicited AEs, the footnote has been added for clarification.
		Section 9.1.2.1 Superiority of vaccine effectiveness of the CCI vaccine CCI when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenB) Section 9.1.2.2 Immunological non-inferiority of CCI vaccine CCI when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenACWY) Section 9.4.2 Primary endpoint(s) – Phase II (Formulation and Schedule-finding)	The confidence interval for the primary immunogenicity objectives associated with phase II formulation and schedule-finding has been changed to 97.5% CI (from 95% CI).	In the statistical analyses of the study, the alpha has been split due to the decision to parallelly test the 2 formulations (CCI). Therefore, the confidence interval for the evaluation of primary endpoints should be presented as 97.5%.
		Section 9.2, Sample size determination	The following sentence added: Participants who withdraw from the study will not be replaced	Clarification added to make it clear that withdrawals will not be replaced in the study.

10.10.1. Protocol amendment 4

Detailed description of *current* Protocol amendment: *New text is shown in bold italics and deleted text is shown in strikethroughs.*

In Section 1.3 Schedule of activities (SoA)

Table 5 Schedule of Activities – Phase II (Sourcing; ***0, 1 month vaccination schedule***)

Table 6 Schedule of Activities – Phase II (Sourcing; 0, 2 month vaccination schedule)

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 9 for visit windows]	*Day 1*	*Day 31*	*Day 61*	*Day 76*	*Day 91*	*Day 181*	*Day 241*	
Informed consent	●							*Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details*
Check inclusion/exclusion criteria	●		○					*Prior to administering each study intervention, the investigator must check eligibility criteria for subsequent vaccinations and criteria for delay of study intervention administration. See Sections 5.1 and 5.2 for inclusion and exclusion criteria*
Study group and treatment number allocation (randomisation)	●							*See Section 6.3 for more information*
Treatment number allocation for subsequent doses			○					
Collect demographic data	●							*See Section 8.2.1.1 for more information*
Medical and vaccination history	●							*See Section 8.2.1.2 for more information*
General physical examination	○							*Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information*
Symptom-directed physical examination			○	○	○			
Check contraindications, warnings and precautions to study intervention administration	○		○					*See Sections 7.1.1 and 8.2.1.5 for more information*

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 9 for visit windows]	*Day 1*	*Day 31*	*Day 61*	*Day 76*	*Day 91*	*Day 181*	*Day 241*	
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○		○	○	○			*See Section 5.5 for more information*
Urine pregnancy test for females	●		●					*See Section 8.2.1.4 for more information*
Body temperature before study intervention administration	●		●					*Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF*
Blood sampling	●^			●	●			*Blood volume of approximately 95 mL will be collected at each blood sampling visit. See Section 8.1.1.1 for more information*
Study intervention administration	●		●					*See Section 6.1 for more information*
Recording of administered study intervention number	●		●					
Post-injection assessment (30 minutes)	●		●					*See Section 10.3.8.1 for more information*
Distribution of eDiary	○							
Review of eDiary		●		●	●			
Return of eDiary					●			
Recording of solicited AEs (Days 1–7 post-vaccination)	*x*		*x*					*See Section 10.3.8 for more information*
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●		●					*See Section 10.3.8 for more information*
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	*Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered See Section 6.8 for more information*
Record any intercurrent medical conditions		●	●	●	●	●	●	*See Section 9.3.1 for more information*
Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs[*]	●	●	●	●	●	●	●	*See Section 10.3.8 for more information*
Recording of SAEs related to study participation, or to a concurrent GSK medication/ vaccine	●	●	●	●	●	●	●	*Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end. See Section 10.3.8 for more information*
Study (Phase II, Sourcing) Conclusion							●	*Participants who terminate the study early are recommended to complete certain study-related procedures. See Section 4.4 and 10.1.9.1 for more information*

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

○ *is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents*
× *is used to indicate a study procedure that will be documented in the eDiary*
^ *Procedure to be performed prior to study intervention administration*
Abbreviation: PC, phone contact; V, clinic visit; T, telephone call; AE, adverse event; SAE, serious adverse event; AESI, adverse events of special interest. Note: All procedures to be performed prior to study intervention administration (as applicable).
** Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 10.3 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 36). In addition, separate COVID-19 specific eCRF form(s) should be completed*
Note 1: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details
Note 2: Refer to Section 8 for information on study procedures during special circumstances

Table 7 Schedule of Activities – Phase II (Sourcing; 0, 6 month vaccination schedule)

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 10 for visit windows]	*Day 1*	*Day 31*	*Day 181*	*Day 196*	*Day 211*	*Day 301*	*Day 361*	
Informed consent	●							*Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details*
Check inclusion/exclusion criteria	●		○					*Prior to administering each study intervention, the investigator must check eligibility criteria for subsequent vaccinations and criteria for delay of study intervention administration. See Sections 5.1 and 5.2 for inclusion and exclusion criteria*
Study group and treatment number allocation (randomisation)	●							*See Section 6.3 for more information*
Treatment number allocation for subsequent doses			○					
Collect demographic data	●							*See Section 8.2.1.1 for more information*
Medical and vaccination history	●							*See Section 8.2.1.2 for more information*
General physical examination	○							*Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information*
Symptom-directed physical examination			○	○	○			

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 10 for visit windows]	*Day 1*	*Day 31*	*Day 181*	*Day 196*	*Day 211*	*Day 301*	*Day 361*	
Check contraindications, warnings and precautions to study intervention administration	○		○					*See Sections 7.1.1 and 8.2.1.5 for more information*
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○		○	○	○			*See Section 5.5 for more information*
Urine pregnancy test for females	●		●					*See Section 8.2.1.4 for more information*
Body temperature before study intervention administration	●		●					*Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF*
Blood sampling	●^			●	●			*Blood volume of approximately 95 mL will be collected at each blood sampling visit.* *See Section 8.1.1.1 for more information*
Study intervention administration	●		●					*See Section 6.1 for more information*
Recording of administered study intervention number	●		●					
Post-injection assessment (30 minutes)	●		●					*See Section 10.3.8.1 for more information*
Distribution of eDiary	○							
Review of eDiary		●		●	●			
Return of eDiary					●			
Recording of solicited AEs (Days 1–7 post-vaccination)	*x*		*x*					*See Section 10.3.8 for more information*
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●		●					*See Section 10.3.8 for more information*
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	*Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered* *See Section 6.8 for more information*
Record any intercurrent medical conditions		●	●	●	●	●	●	*See Section 9.3.1 for more information*
Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs[*]	●	●	●	●	●	●	●	*See Section 10.3.8 for more information*
Recording of SAEs related to study participation, or to a concurrent GSK medication/ vaccine	●	●	●	●	●	●	●	*Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end.* *See Section 10.3.8 for more information*

Type of contact	*Visit*	*PC*	*Visit*	*Visit*	*Visit*	*PC*	*PC*	*Notes*
Visit/Phone call no.	*V1*	*T1*	*V2*	*V3*	*V4*	*T2*	*T3*	
Timepoint(s) [refer to Table 10 for visit windows]	*Day 1*	*Day 31*	*Day 181*	*Day 196*	*Day 211*	*Day 301*	*Day 361*	
Study (Phase II, Sourcing) Conclusion							●	*Participants who terminate the study early are recommended to complete certain study-related procedures. See Section 4.4 and 10.1.9.1 for more information*

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF. Documentation will be required in the source documents
× is used to indicate a study procedure that will be documented in the eDiary
^ Procedure to be performed prior to study intervention administration
Abbreviation: PC, phone contact; V, clinic visit; T, telephone call; AE, adverse event; SAE, serious adverse event; AESI, adverse events of special interest. Note: All procedures to be performed prior to study intervention administration (as applicable).
** Diagnosis of coronavirus 2019 (COVID-19) should be made in accordance with the World Health Organization case definitions. Cases should be reported as AEs or SAEs (refer to Section 10.3 for the definitions), and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the protocol-defined time periods (refer to Table 36). In addition, separate COVID-19 specific eCRF form(s) should be completed*
Note 1: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details
Note 2: Refer to Section 8 for information on study procedures during special circumstances

Table 8 Intervals between study visits/contacts – Phase II (Sourcing; ***0, 1 month vaccination schedule)***

Table 9 Intervals between study visits/contacts – Phase II (Sourcing; 0, 2 month vaccination schedule)

Interval	*Planned visit interval*	*Allowed interval range (visit window)*
Visit 1 → Telephone contact T1	*30 days*	*23 to 44 days (-7 to +14 days)*
Visit V1 → Visit V2	*60 days*	*74 days (+14 days)*
Visit V2 → Visit V3	*15 days*	*10 to 22 days (-5 to +7 days)*
Visit V2 → Visit V4	*30 days*	*25 to 51 days (-5 to +21 days)*
Visit V2 → Telephone contact T2	*120 days*	*113 to 134 days (-7 to +14 days)*
Visit V2 → Telephone contact T3	*180 days*	*173 to 194 days (-7 to +14 days)*

Table 10 Intervals between study visits/contacts – Phase II (Sourcing; 0, 6 month vaccination schedule)

Interval	*Planned visit interval*	*Allowed interval range (visit window)*
Visit 1 → Telephone contact T1	*30 days*	*23 to 44 days (-7 to +14 days)*
Visit V1 → Visit V2	*180 days*	*194 days (+14 days)*
Visit V2 → Visit V3	*15 days*	*10 to 22 days (-5 to +7 days)*
Visit V2 → Visit V4	*30 days*	*25 to 51 days (-5 to +21 days)*
Visit V2 → Telephone contact T2	*120 days*	*113 to 134 days (-7 to +14 days)*
Visit V2 → Telephone contact T3	*180 days*	*173 to 194 days (-7 to +14 days)*

In Section 3, Objectives and endpoints:

Table 11 Study objective(s) and endpoints

Phase II –Sourcing	
Primary	

To evaluate the safety and reactogenicity of the 2 formulations (CCI) of the CCI vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination ~~at Day 1 and Day 31 in all groups~~:
	  • Day 1 and Day 31 in C ***groups,***
	  • ***at Day 1 and Day 61 in*** C ***groups, and***
	  • ***at Day 1 and Day 181 in*** C ***groups.***
	• The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at ~~Day 1 and Day 31 in all groups~~:
	  • Day 1 and Day 31 C ***groups,***
	  • ***at Day 1 and Day 61 in ABCWY50S_02 and*** CCI ***groups, and***
	  • ***at Day 1 and Day 181 in*** C ***groups***.
	• The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period ~~in all groups (Day 1 through Day 211)~~***:***
	  • Day 1 through Day 211 ***in*** C ***groups,***
	  • ***Day 1 through Day 241 in*** C ***groups, and***
	  • ***Day 1 through Day 361 in*** C ***groups***).

C [redacted]	

In Section 4.1.2.2 Phase II Sourcing

The blood sourcing part of the Phase II study will include 2 groups (randomised 1:1), with a parallel enrolment of a total of 226* participants (~~Figure 3~~):

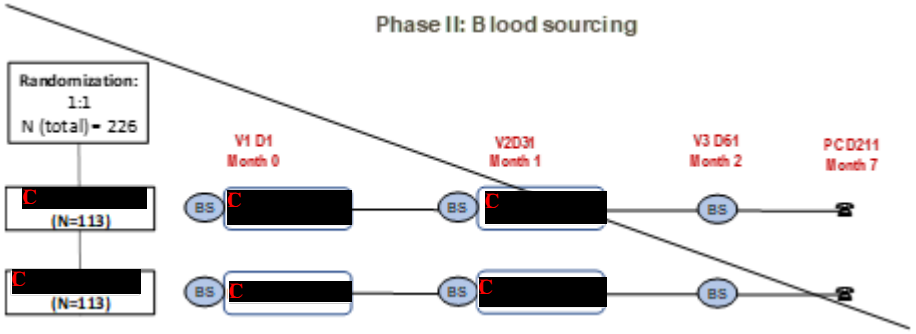
- : Participants will receive 2 vaccinations of the vaccine in a (0,1-month) schedule.
- : Participants will receive 2 vaccinations of the vaccine in a (0,1-month) schedule.

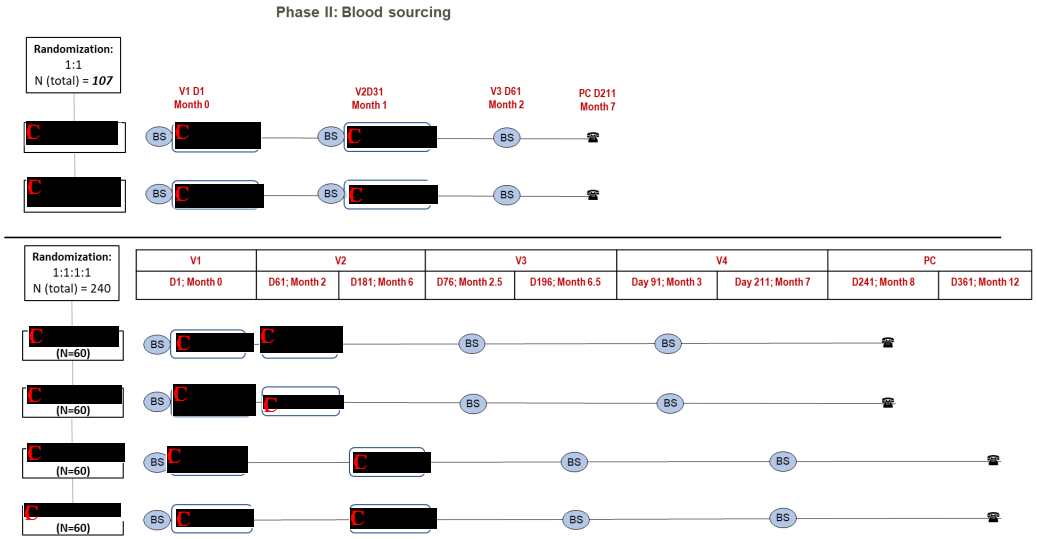
**** At the time of this protocol amendment (Protocol amendment 4), enrolment to these 2 groups had been stopped. The total number of participants enrolled have been presented in Figure 3.***

Additionally, the Phase II sourcing part will include 4 more groups (randomised 1:1:1:1), with a parallel enrolment of a total of 240 participants (Figure 3):

- ***: Participants will receive 2 vaccinations of the vaccine in a (0,2-month) schedule.***
- ***: Participants will receive 2 vaccinations of the vaccine in a (0,2-month) schedule.***
- ***: Participants will receive 2 vaccinations of the vaccine in a (0,6-month) schedule.***
- ***: Participants will receive 2 vaccinations of the vaccine in a (0,6-month) schedule.***

Figure 3 Study design overview – Phase II (Sourcing)





Note 1: This figure represents the main aspects of the study design. Refer to Table 5, ***Table 6 and Table 7***, Schedule of activities, for details on all visits and contacts
Note 2: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Refer to the SoA (Table 5, ***Table 6 and Table 7***) for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details

Table 14 Study groups, intervention and blinding – Phase II (Sourcing)

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
C [redacted]	~~113~~ ~~113~~ ***107***	18-50 yoa	C [redacted]	Observer-blinded*
	60			
	60			
	60			
	60			

**** Due to the different vaccination schedules in Phase II Sourcing, the study will be observer blind only in terms of the vaccine formulations.***

Duration of the Phase II (Sourcing) of the study: The intended duration of the Phase II (sourcing) of the study, per participant is:

- approximately 7 months ***for the*** C [redacted] ***and*** C [redacted] ***groups***,
- ***approximately 8 months for the*** C [redacted] ***and*** C [redacted] ***groups, and,***
- ***approximately 12 months for the*** C [redacted] ***and*** C [redacted] ***groups.***

Data collection: Standardised Electronic Case Report Form (eCRF). Solicited events will be collected using a participant diary (electronic Diary [eDiary]).

Sampling schedule for Phase II (Sourcing) of the study:

- Blood sample: Refer to Section 8.1.1.1 for details on collection of blood samples.
- Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential ~~at Visit 1 (Day 1) and Visit 2 (Day 31)~~ prior to the study intervention ***(at the following timepoints):***
  - ***at Visit 1 (Day 1) and Visit 2 (Day 31) for the*** C [redacted] ***groups,***
  - ***at Visit 1 (Day 1) and Visit 2 (Day 61) for the*** C [redacted] ***groups, and,***
  - ***at Visit 1 (Day 1) and Visit 2 (Day 181) for the*** C [redacted] ***groups.***

In Section 4.2 Scientific rationale for study design:

- The second part of the study [**Phase II** (Figure 2 ***and Figure 3***] will only commence after demonstration of acceptable safety and reactogenicity in Phase I participants (Section 4.1.1). This Phase II will have 2 components – the formulation and schedule-finding part and the blood sourcing part.

The 0,1-month schedule was selected for Phase I and Phase II (Sourcing) because the short time interval between vaccinations is conservative for the assessment of reactogenicity and safety.

Furthermore, the CCI vaccine will also be administered according to a 0,2month or 0,6month interval (wider dosing schedules) in the Phase II Sourcing part to support the finalization of assay development, further clinical testing, as well as assay stability monitoring and maintenance. For this reason, the total sample size of subjects in the Phase II Sourcing have been increased.

In Section 4.4 End of study definition:

A participant is considered to have completed the study if he/she returns for the last visit or is available for the last scheduled contact/ visit as described in the protocol ***[***Telephone T3 in Phase I, Visit V6 in Phase II, Formulation and Schedule-finding and Telephone T2 ***or Telephone T3*** in Phase II, Sourcing ***(as per the group allocation)]***.

End of Study (EoS): Date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after Last Subject Last Visit (LSLV) (LSLV = Day 541, Month 18 in Phase II, formulation and schedule-finding). ***If the completion of testing occurs prior the completion of the LSLV the latter date defines the end of study visit.***

In Section 5.5, Criteria for temporarily delaying enrolment/ randomisation/ study intervention administration/blood sampling:

- Significant acute illness within the previous 7 days ***of study intervention administration***.
- A positive test for current infection with COVID-19 ***prior to intervention administration***. The testing should have been done using a molecular (polymerase chain reaction [PCR] or antigen test) approved by the country regulatory authorities.
- Participants with known COVID-19 positive contacts ***and considered at risk of having contracted a COVID-19 infection according to local regulations***.

In Section 6.1, Study intervention(s) administered:

Table 17 Study intervention administered – Phase II (Sourcing)

Study intervention name:	C	
No of doses		
C	2	-
	-	2
	2	**-**
	-	**2**

Study intervention name:	[redacted]	
[redacted]	2	-
	-	2

In Section 6.3.5 Blinding and unblinding:

6.3.5.1 Phase I and Phase II (Sourcing)

Data will be collected in an observer-blind manner. To do so, study intervention(s) will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety, efficacy).

Note: Due to the different vaccination schedules in Phase II Sourcing, the study will be observer blind only in terms of the vaccine formulations

6.3.5.3 Unblinding

The participant, the site and sponsor personnel involved in the clinical evaluation of the participants will be unblinded to the treatment assigned at a Phase at completion of that particular Phase.

Refer to Section 4.4 for the definition of study completion per participant.

In Section 6.6, Continued access to study intervention after the end of the study:

During the study conclusion visit/contact (Telephone T3 in Phase I, Visit V6 in Phase II, Formulation and Schedule-finding and Telephone T2***/ Telephone T3*** in Phase II, Sourcing ***[as per group allocation]***), the investigator will ask each participant/participant's parent(s)/LAR(s) if they are interested in participating/allowing the participant to join a booster study/long-term study. If a participant/participant's parent(s)/LAR(s) is/are not interested in joining the booster study/long-term study the reason for refusal will be documented, when available, in the participant's eCRF.

In Section 6.8 Concomitant therapy:

- All concomitant medication associated with an adverse event, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention (Phase 1 and Phase II, Sourcing: Day 1 to Day 211 ***or Day 241 or Day 361 (as per the group allocation)*** and Phase II, Formulation and Schedule-finding: Day 1 to Day 541).
- Any concomitant vaccination administered in the period starting 14 days before the first dose of study intervention and ending at the last study contact (Phase 1 and Phase II, Sourcing: -Day 14 to Day 211 ***or Day 241 or Day 361 (as per the group allocation)*** and Phase II, Formulation and Schedule-finding: Day -14 to Day 541).

In Section 8, Study assessments and procedures:

Study procedures in special circumstances:

- If despite best efforts it is not possible to collect the biological samples within the interval pre-defined in the protocol (see Table 2 for Phase I, Table 4 for Phase II, Formulation and Schedule-finding and Table 8, ***Table 9 and Table 10*** for Phase II, Sourcing), then the applicable intervals may be extended up to a maximum length of days as presented in Table 19 (Phase I), Table 20 (Phase II, Formulation and Schedule-finding) and Table 21, ***Table 22 and Table 23*** (Phase II, Sourcing), as applicable.
- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Table 2 for Phase I, Table 4 for Phase II, Formulation and Schedule-finding and Table 8, ***Table 9 and Table 10*** for Phase II, Sourcing), a maximum dose interval may be used as presented in Table 19 (Phase I) and Table 20 (Phase II, Formulation and Schedule-finding) and Table 21, ***Table 22 and Table 23*** (Phase II, Sourcing), as applicable.

Table 21 Intervals between study visits/contacts during special circumstances – Phase II (Sourcing; ***0,1 month vaccination schedule*****)**

Table 22 Intervals between study visits/contacts during special circumstances – Phase II (Sourcing; 0,2 month vaccination schedule)

Interval	*Length of interval*	*Allowed interval (Visit window)*
Visit V2 → Visit V3	*15 days*	*8 to 22 days (-7 to +7 days)*
Visit V2 → Visit V4	*30 days*	*25 to 51 days (-5 to +21 days)*
Visit V2 → Telephone contact T2	*120 days*	*113 to 141 days (-7 to +21 days)*
Visit V2 → Telephone contact T3	*180 days*	*173 to 201 days (-7 to +21 days)*

Table 23 Intervals between study visits/contacts during special circumstances – Phase II (Sourcing; 0,6 month vaccination schedule)

Interval	*Length of interval*	*Allowed interval (Visit window)*
Visit V2 → Visit V3	*15 days*	*8 to 22 days (-7 to +7 days)*
Visit V2 → Visit V4	*30 days*	*25 to 51 days (-5 to +21 days)*
Visit V2 → Telephone contact T2	*120 days*	*113 to 141 days (-7 to +21 days)*
Visit V2 → Telephone contact T3	*180 days*	*173 to 201 days (-7 to +21 days)*

In Section 8.1.1.1 Blood sample

Phase II (sourcing): An overall blood volume of approximately 285 mL per participant will be collected over the course of the Phase II, Sourcing part of the study. Please refer to Table 25 and ***Table 26*** for details.

Table 25 Blood samples at Phase II (Sourcing; *0,1 month vaccination schedule*)

Sample type	Quantity	Unit	Timepoint	Subset name/ Group	Day
Blood	Approximately 95	mL	Visit V1 (CCI);	All participants	Day 1
Blood	Approximately 95	mL	Visit V2 (CCI	All participants	Day 31
Blood	Approximately 95	mL	Visit V3 (CCI	All participants	Day 61

Pre-Vacc, Pre-vaccination timepoint; Post-Vacc, Post-vaccination timepoint

Refer to Table 5 (SoA for Phase II, Sourcing) for details of visits.

Table 26 Blood samples at Phase II (Sourcing; 0,2 and 0,6 month vaccination schedule)

Sample type	*Quantity*	*Unit*	*Timepoint*	*Subset name/ Group*	*Day*
Blood	*Approximately 95*	*mL*	*Visit V1 CCI ;*	*All participants*	*Day 1*
Blood	*Approximately 95*	*mL*	*Visit V3 (CCI);*	CCI	*Day 76*
					Day 196
Blood	*Approximately 95*	*mL*	*Visit V4 (CCI*		*Day 91*
					Day 211

Pre-Vacc, Pre-vaccination timepoint; Post-Vacc, Post-vaccination timepoint.
Refer to Table 6 and Table 7(SoA for Phase II, Sourcing) for details of visits.

In section 8.1.2 Laboratory assays:

Effectiveness of the CCI antigens of the CCI vaccine will be evaluated with serum bactericidal assays using endogenous source of human complement (enc-hSBA), on a panel of 110 US representative *N. meningitidis* serogroup B invasive disease strains. Immunogenicity of the vaccine against serogroups A, B, C, W and Y will be evaluated with the serum bactericidal assay using exogenous source of human complement (hSBA). An ~~enzyme-linked immunosorbent assay (ELISA) or any other ELISA-like technology~~ CCI ***multiplex assay*** will be used to evaluate the serotype-specific IgG responses to A, C, W, and Y.

Table 28 Laboratory assays – Phase I and II

CCI

CCI [redacted]

In Section 8.1.3, Immunological read-outs:

Table 29 Immunological read-outs – Phase II (Formulation and Schedule-finding), 0_6 schedule: For CCI [redacted] and Control groups

CCI [redacted]

Table 31 Immunological read-outs – Phase II (Sourcing): CCI [redacted] *groups*

CCI [redacted]

In Section 8.3.1, Time period and frequency for collecting AE, SAE and other safety information:

Table 36 Timeframes for collecting and reporting of safety information – Phase II (Sourcing ***0,1 month vaccination schedule***)

Table 37 Timeframes for collecting and reporting of safety information – Phase II (Sourcing; 0,2 month vaccination schedule)

Event	*On V1**	*V1*		*V2*		*V3*	*V4*	*PC*	*Phase II, Sourcing conclusion*
		*D1****	*D7*	*D61*	*D67*	*D76*	*D91*	*Day 181*	*D 241 (PC)*
Solicited administration site and systemic events									
*Unsolicited AEs***									
*AEs leading to withdrawal from the study***									
*SAEs***									
SAEs related to study participation or concurrent GSK medication/vaccine									
*AESIs***									
*Pregnancies***									

** i.e. consent obtained.; V: Visit; D: Day, M: Month; PC=Phone call*
*** Including COVID-19 infection-related AEs; Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination)*
**** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration*

Table 38 Timeframes for collecting and reporting of safety information – Phase II (Sourcing; 0,6 month vaccination schedule)

Event	On V1*	V1		V2		V3	V4	PC	Study conclusion
		D1***	D7	D181	D187	D196	D211	Day 301	D 361(PC)
Solicited administration site and systemic events									
Unsolicited AEs**									
AEs leading to withdrawal from the study**									
SAEs**									
SAEs related to study participation or concurrent GSK medication/vaccine									
AESIs**									
Pregnancies**									

** i.e. consent obtained.; V: Visit; D: Day, M: Month; PC=Phone call*
*** Including COVID-19 infection-related AEs; Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination)*
**** Except SAEs related to study participation or concurrent GSK medication/vaccine, all other safety data will be collected starting from Visit 1 after vaccine administration*

In Section 9.2.3, Phase II (Sourcing):

~~Two hundred and twenty-six (226)~~ ***One hundred and seven (107)*** participants ~~are to be~~ ***have been*** enrolled in 2 arms of Phase II (Sourcing) of the study, 113 participants each in C group (1:1 randomisation). ***At the time of this amendment (Protocol amendment 4) enrolment to these groups was stopped.***

Two hundred and forty (240) participants are to be enrolled in 4 arms, 60 participants each in C groups (1:1:1:1 randomization).

In Section 9.3, Analysis sets:

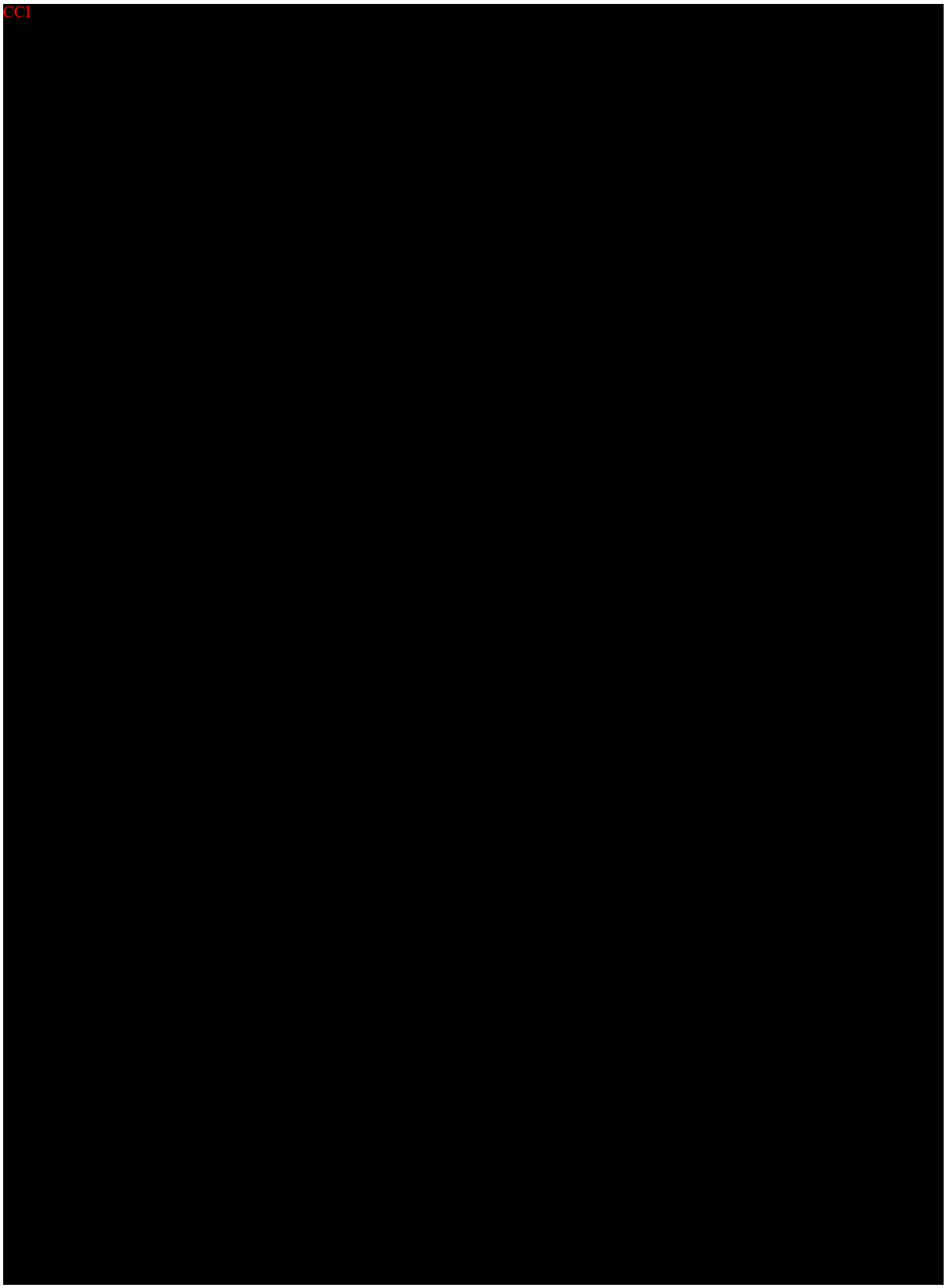
CCI

In Section 9.4.3, Primary endpoint(s) – Phase II (Sourcing)

Primary Endpoint	Statistical Analysis Methods
Safety	CCI

CCI

CCI



In Section 10.1.9.1, Study conclusions:

At Phase I conclusion phone call (Day 211), Phase II (Formulation and Schedule-finding) conclusion visit (study conclusion; Visit 6, Day 541) and Phase II (Sourcing) conclusions

phone call (Day 211 ***in*** C [redacted] ***groups and Day 361 in*** C [redacted] ***groups***), the investigator will:

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

CCI [redacted]

In Section 10.3.8, Recording and follow-up of AEs, SAEs, AESIs and pregnancies:

- Verify completed eDiaries during discussions with the participant/participant's parent(s)/LAR(s) on:
  - Visit *V*3 (Day 31) and Visit *V*4 (Day 61) – Phase I
  - Visit *V*2 (Day 31), Visit *V*4 (Day 181) and Visit *V*5 (Day 211) – Phase II, Formulation and Schedule finding, C [redacted] groups
  - Visit *V*2 (Day 31) and Visit *V*5 (Day 211) – Phase II, Formulation and Schedule finding, Control group
  - Visit *V*2 (Day 31) and Visit *V*3 (Day 61) – Phase II, Sourcing, C [redacted] ***groups.***

- ***Phone call (T1, Day 31), Visit V3 (Day 76) and Visit 4 (Day 91) – Phase II, Sourcing,C groups.***
- ***Phone call (T1, Day 31), Visit V3 (Day 196) and Visit 4 (Day 211) - Phase II, Sourcing,C groups.***

Collect eDiaries on Visit 4 (Day 61) for Phase I participants, Visit 5 (Day 211) for Phase II (Formulation and Schedule-finding) participants and Visit 3*/4* (***V3,*** Day 61 ***for C groups, V4, Day 91 for C groups and V4, Day 211 in C groups***) for Phase II (Sourcing) participants.

In Section 10.3.9.3, Medically attended visits:

For each solicited and unsolicited AE the participant experiences (Refer to Table 34, Table 35, Table 36, ***Table 37 and Table 38***), the participant/participant's parent(s)/LAR(s) will be asked if he/she/the participant received medical attention (defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the eDiary/ eCRF.

In Section 10.3.9.5, Recording of AEs related to COVID-19:

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

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

Note: Due to the rapid evolution of the COVID-19 pandemic situation, it is important to adhere to the most recent guidelines released by WHO. Please refer to the WHO website for the latest guidance.

- Confirmed COVID-19 case ***[WHO, 2020]***

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

In Section 10.5.1.1.1, Women not considered as women of childbearing potential:

- **Premenopausal female with ONE of the following:**
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - ***Current bilateral tubal ligation or occlusion***

10.10.2. Protocol amendment 3

Detailed description of *current* Protocol amendment: *New text is shown in bold italics and deleted text is shown in strikethroughs.*

In Section 1.3 Schedule of activities, Table 1, Schedule of Activities – Phase I:

Type of contact	Visit	Visit	Visit	PC	Visit	PC	*PC*	Notes
Visit/Phone call no.	V1	V2	V3	T1	V4	T2	*T3*	
Timepoint(s) [refer to Table 2 for visit windows]	Day 1	Day 8	Day 31	Day 38	Day 61	Day 151	*Day 211*	
Blood sampling for sourcing	●^		●^		●			Blood volume of ***approximately*** 80 mL will be collected at each blood sampling visit. See Section 8.1.1.1 for more information

In Section 1.3 Schedule of activities, Table 2, Intervals between study visits/contacts –Phase I:

Interval	Planned visit/ phone call interval	Allowed interval range (visit window)
Visit V3 → Telephone contact T1	~~6~~ ***7*** days	~~5~~ ***6*** to ~~7~~ ***8*** days (-1 to +1 days)

In Section 1.3 Schedule of activities, Table 3, Schedule of Activities – Phase II (Formulation and schedule-finding):

Type of contact	Visit	PC	Visit	PC	Visit	***PC***	Visit	Visit	PC	PC	PC	Visit	Notes
Visit/Phone call no.	V1	T1	V2	T2	***V3†***	***TC††***	V4	V5	T3	T4	T5	V6	
Timepoint(s) [refer to Table 4 for visit windows]	Day 1	Day 8**	Day 31	Day 91	Day 121	***Day 121***	Day 181	Day 211	Day 271	Day 361	Day 451	Day 541	
Groups	***All***	***First 45****	***All***	***All***	***ABCWY groups***	***Control group***	***All***	***All***	***All***	***All***	***All***	***All***	
Informed consent	●												Confirm consent form signed prior to any procedures. Before performing any study-related activities, check the randomisation system to ensure that enrolment is still open See Section 10.1.3 for details
Informed assent, if applicable	○												Confirm assent form (if applicable) signed prior to any procedures
Check inclusion/exclusion criteria	●				○		○						Prior to administering each study intervention the investigator must check eligibility criteria for subsequent vaccination and criteria for delay of study intervention administration See Sections 5.1 and 5.2 for inclusion and exclusion criteria

Type of contact	Visit	PC	Visit	PC	Visit	***PC***	Visit	Visit	PC	PC	PC	Visit	Notes
Visit/Phone call no.	V1	T1	V2	T2	***V3†***	***TC††***	V4	V5	T3	T4	T5	V6	
Timepoint(s) [refer to Table 4 for visit windows]	Day 1	Day 8**	Day 31	Day 91	Day 121	***Day 121***	Day 181	Day 211	Day 271	Day 361	Day 451	Day 541	
Groups	***All***	***First 45****	***All***	***All***	***ABCWY groups***	***Control group***	***All***	***All***	***All***	***All***	***All***	***All***	
Study group and treatment number allocation (randomisation)	●												See Section 6.3 for more information
Treatment number allocation for subsequent doses					○		○						
Collect demographic data	●												See Section 8.2.1.1 for more information
Medical and vaccination history	●												See Section 8.2.1.2 for more information
General physical examination	○												Physical examination to be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Delegation of Responsibility Log. See Section 8.2.1.3 for more information
Symptom-directed physical examination			○		○		○	○				○	
Check contraindications, warnings and precautions to study intervention administration	○				○		○						See Sections 7.1.1 and 8.2.1.5 for more information
Check criteria for temporary delay for enrolment/study intervention administration/blood sampling	○		○		○		○	○				○	See Section 5.5 for more information
Urine pregnancy test for females of childbearing potential	●				●		●						See Section 8.2.1.4 for more information
Body temperature before study intervention administration	●				●		●						Fever is defined as temperature ≥38.0°C/100.4°F. Preferred location for measuring temperature will be the oral cavity. If any other route is used for measuring temperature, this needs to be recorded in the eCRF
Blood sampling	●^		●					●				●	Blood volume of ***approximately*** 15 mL will be collected at V1 (pre-vaccination) and V2 and ***approximately*** 30 mL at V5 and V6. See Section 8.1.1.1 for more information
Study intervention administration	●				●		●						See Section 6.1 for more information
Recording of administered study intervention number	●				●		●						

Type of contact	Visit	PC	Visit	PC	Visit	***PC***	Visit	Visit	PC	PC	PC	Visit	Notes
Visit/Phone call no.	V1	T1	V2	T2	**V3†**	***TC††***	V4	V5	T3	T4	T5	V6	
Timepoint(s) [refer to Table 4 for visit windows]	Day 1	Day 8**	Day 31	Day 91	Day 121	***Day 121***	Day 181	Day 211	Day 271	Day 361	Day 451	Day 541	
Groups	***All***	***First 45****	***All***	***All***	***ABCWY groups***	***Control group***	***All***	***All***	***All***	***All***	***All***	***All***	
Post-injection assessment (30 minutes)	●				●		●						See Section 10.3.8.1 for more information
Distribution of eDiary	○				○		○						
Review of eDiary		●	●				●‡	●					
Return of eDiary								●					
Recording of solicited AEs (Days 1–7 post-vaccination)	x				x		x						See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1-30 post-vaccination)	●	●	●		●		●	●					See Section 10.3.8 for more information
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●	●	●	●	Timeframe for recording of concomitant medications/vaccinations is according to the recording period of the AEs for which they are being administered. See Section 6.8 for more information
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●	See Section 9.3.1 for more information
Recording of any AEs leading to vaccine/study withdrawal, SAEs, pregnancies and AESIs*	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	●	Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine begins from the time a participant signs the consent form to the study end. See Section 10.3.8 for more information
Study Conclusion												●	Participants who terminate the study early are recommended to complete certain study-related procedures See Section 4.4 and 10.1.9.1 for more information

TC, Telephone contact for Control group only

† Visit V3 (at Day 121) is only applicable for C groups

†† TC (at Day 121) is only applicable for the Control group

‡ Not applicable for Control group

In Section 1.3 Schedule of activities, Table 4, Intervals between study visits/contacts –Phase II (Formulation and schedule-finding):

Interval	Planned visit interval	Allowed interval range
Visit V1→Telephone contact T1*	7 days	6 to 8 days (-1 to +1 days)
Visit V2 →Visit V3/***TC*****	90 days	85 to 104 days (-5 to +14 days)
Visit V3/***TC*****→ Visit V4	60 days	55 to 74 days (-5 to +14 days)
Visit V4 → Telephone contact T3	90 days	83 to 104 days (-7 to +14 days)
Visit V4 → Telephone contact T4	180 days	173 to 194 days (-7 to +14 days)
Visit V4 → Telephone contact T5	270 days	263 to 284 days (-7 to +14 days)

TC, Telephone contact for Control group only
**** The phone call (T1) at Day 8 is only for the first 45 participants (15 participants in C , 5 participants in C , 15 participants in C 5 participants in C and 5 participants in the Control groups).***
***** Visit for C groups (Visit V3) and telephone call for Control group (TC)***

In Section 1.3 Schedule of activities, Table 5, Schedule of Activities – Phase II (Sourcing):

Type of contact	Visit	Visit	Visit	PC	PC	Notes
Visit/Phone call no.	V1	V2	V3	T1	T2	
Timepoint(s) [refer to Table 6 for visit windows]	Day 1	Day 31	Day 61	Day 151	Day 211	
Blood sampling	●^	●^	●			Blood volume of ***approximately*** 95 mL will be collected at each blood sampling visit. See Section 8.1.1.1 for more information

In Section 2.3 Benefit/Risk assessment

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 (as per the phase in which they are participating: Visit V1 and Visit V3 in Phase I, Visit V1, Visit V3^ and Visit V4 in Phase II Formulation and Schedule-Finding and Visit V1 and Visit V2 in Phase II Sourcing). Refer to Section 6.1.

^ ***except for Control group participants who will have a phone call at this time point (TC).***

In Section 3, Table 7, Study objective(s) and endpoints

Objectives	Endpoints
Phase II – Formulation and Schedule-finding	
Primary	
To evaluate the safety and reactogenicity of the CCI vaccine (C), the MenB vaccine and the MenACWY vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at: • Day 1, Day 121 and Day 181 ***in the*** C

Objectives	Endpoints
	C ***groups, and*** • ***Day 1 and Day 181 in the Control group***. • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at: • Day 1, Day 121 and Day 181 ***in the*** C ***groups, and*** • ***Day 1 and Day 181 in the Control group***. • The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 541).

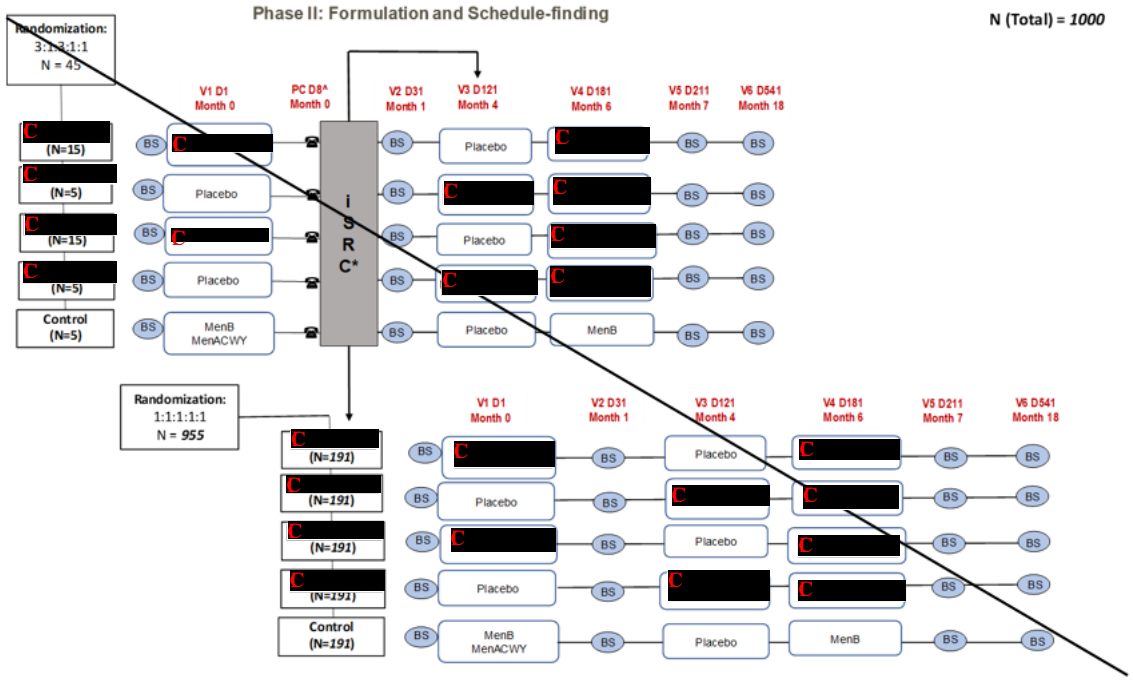
Note 1: MenB immune response will be assessed against *N. meningitidis* serogroup B indicator strains C

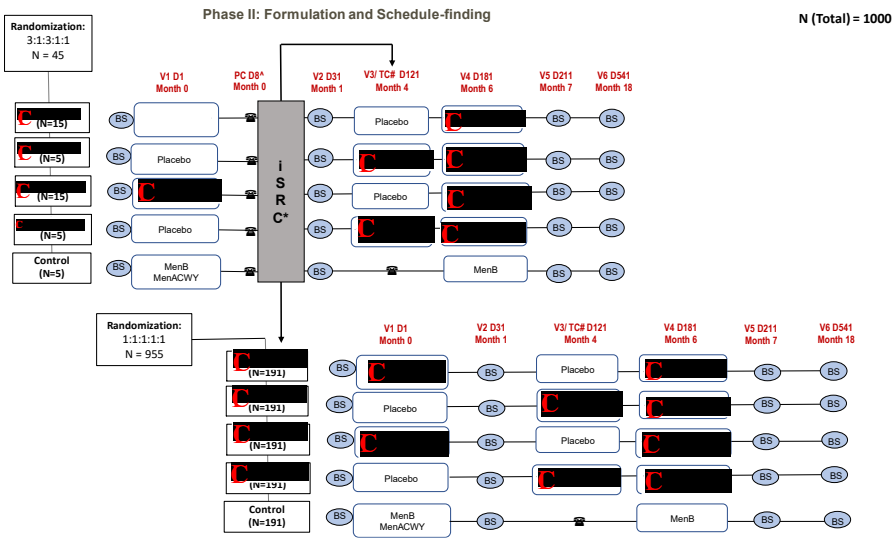
C

In Section 4.1.2.1, Phase II: Formulation and Schedule-finding:

Control: Participants will receive 2 vaccinations of MenB vaccine (*Bexsero*) in a (0,6-months) schedule and a single vaccination of MenACWY vaccine (*Menveo*). ~~They will also receive 1 injection of placebo.~~

Figure 2 Study design overview – Phase II (Formulation and Schedule-finding)





TC, Telephone contact for Control group only
 # Day 121 Month 4 is a visit for C groups (Visit V3) and is a telephone call for Control group (TC)

If the decision is "go", further vaccination at Month 4 and other study procedures following that will continue in these groups ***(as per the study design)*** along with continuing to recruit participants with a randomisation ratio of 1:1:1:1:1 (191 in each group) to reach the target total sample of 955 participants. Refer to Table 9 for total number of participants per group.

Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential at Visit 1 (Day 1), Visit 3 (Day 121) and Visit 4 (Day 181) prior to the vaccination ***in the ABCWY groups and at Visit 1 (Day 1) and Visit 4 (Day 181) prior to the vaccination in the Control group.***

In Section 6.1, Table 12, Study intervention administered – Phase II (Formulation and Schedule-finding)

Study intervention	C		*Bexsero*	*Menveo**	Placebo (saline)
Product category	Combination	Combination	*Combination*	*Biological*	Combination
C	2	-	-	-	1
	2	-	-	-	1
	-	2	-	-	1
	-	2	-	-	1
Control	-	-	2	1	~~1~~
Laterality***	Non-dominant***	Non-dominant***	*Non-dominant****	*Dominant*	Non-dominant***

In Section 8, Table 16, Intervals between study visits during special circumstances – *Phase II (Formulation and Schedule finding)*

Interval	Length of interval	Allowed interval (Visit window)
Visit V1 → Visit V2	30 days	23 to 51 days (-7 to +21 days)
Visit V1 → Telephone contact T2	90 days	83 to 111 days (-7 to +21 days)
Visit V2→Visit V3/*TC**	90 days	83 to 111 days (-7 to +21 days)
Visit V3/*TC** → Visit V4	60 days	53 to 81 days (-7 to +21 days)
Visit V4 → Visit V5	30 days	23 to 51 days (-7 to +21 days)
Visit V4 → Telephone contact T3	90 days	83 to 111 days (-7 to +21 days)
Visit V4 → Telephone contact ~~T3~~ *T4*	180 days	173 to 201 days (-7 to +21 days)
Visit V4 → Telephone contact ~~T4~~ *T5*	270 days	263 to 291 days (-7 to +21 days)
Visit V4→Visit V6	360 days	353 to 381 days (-7 to +21 days)

**** Visit for*** CCI [redacted] ***groups (Visit V3) and telephone call for Control group (TC)***

In Section 8.1.1.1, Blood sample

Phase I: An overall blood volume of ***approximately*** 240 mL per participant will be collected over the course of the Phase I part of the study.

Phase II (sourcing): An overall blood volume of ***approximately*** 285 mL per participant will be collected over the course of the Phase II, Sourcing part of the study.

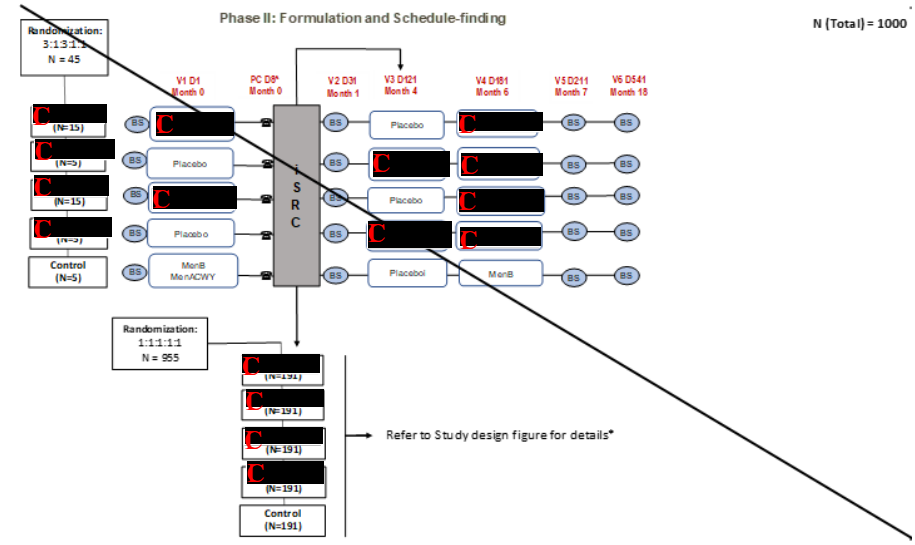
Phase II (formulation and schedule-finding): In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA), an overall blood volume of ***approximately*** 90mL, per participant, will be collected over the course of the Phase II step of the study.

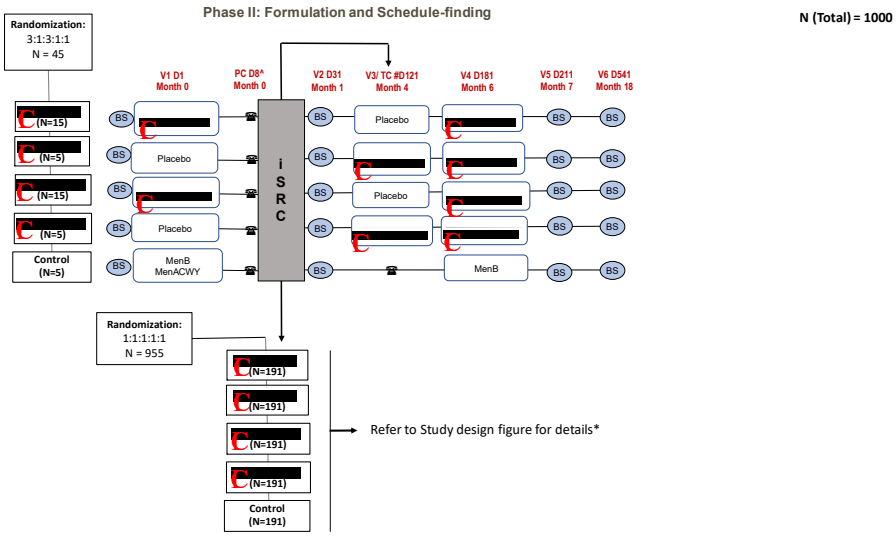
In Section 8.1.3, Table 24 Immunological read-outs – Phase II (Sourcing): All participants:

CCI [redacted]

In Section 8.2.2.1.1 Safety evaluation:

Figure 5 Step-wise approach for safety review in Phase II (Formulation and Schedule-finding)





TC, Telephone contact for Control group only
 # Day 121 Month 4 is a visit for C groups (Visit V3) and is a telephone call for Control group (TC)

The following step-wise approach will be followed for the safety evaluation during the Phase II (Formulation and Schedule-finding):

- If the decision is "go", the enrolment in all groups will continue with a randomisation ratio of 1:1:1:1:1 to the target total sample of 1000 participants and the administration of the second vaccination at Month 4 will take place in the ***40*** participants ***in C groups (as per study design)***.

In Section 8.3.1, Table 27, Timeframes for collecting and reporting of safety information – Phase I:

** Including COVID-19 infection-related AEs; ***Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination***

In Section 8.3.1, Table 28, Timeframes for collecting and reporting of safety information – Phase II (Formulation and schedule-finding)

Event	On V1*	V1	V2	**V3#**	V4	V5	PC	V6 Study Conclusion

#Solicited AEs and unsolicited AEs will be collected only for C groups at Visit V3 (Control group will have a phone call at this time point (TC) where other safety follow-up will be done)
** Including COVID-19 infection-related AEs; ***Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination***

In Section 8.3.1, Table 29, Timeframes for collecting and reporting of safety information – Phase II (Sourcing):

** Including COVID-19 infection-related AEs; ***Recording of unsolicited AEs is only from Day 1 to Day 30 post-vaccination***

In Section 9.1.2.1 Superiority of vaccine effectiveness of the CCI vaccine (C) when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenB)

Superiority of CCI to Control vaccine (MenB) will be demonstrated if the Lower Limit (LL) of the 2-sided ~~95%~~ ***97.5***% Confidence Interval (CI) for the group difference in percentages of samples with bactericidal serum activity against a randomly selected panel is above 5%.

In Section 9.1.2.2 Immunological non-inferiority of CCI vaccine CCI when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenACWY)

Immunological non-inferiority of CCI vaccine to Control (MenACWY) will be demonstrated if the LL of the 2-sided ~~95%~~ ***97.5***% CI for the group difference in percentages of participants achieving a 4-fold rise in hSBA titres is above -10% for each serogroup.

In Section 9.2 Sample size determination

Participants who withdraw from the study will not be replaced.

In Section 9.4.2 Primary endpoint(s) – Phase II (Formulation and Schedule-finding)

Primary Endpoint	Statistical Analysis Methods
Superiority of effectiveness	CCI

Primary Endpoint	Statistical Analysis Methods
	CCI [redacted]
Immunological non-inferiority	
Safety	

In Section 10.3.8 Recording and follow-up of AEs, SAEs, AESIs and pregnancies:

- Verify completed eDiaries during discussions with the participant/participant's parent(s)/LAR(s) on:
  - Visit 3 (Day 31) and Visit 4 (Day 61) – Phase I

- Visit 2 (Day 31), Visit 4 (Day 181) and Visit 5 (Day 211) – Phase II, ***Formulation and Schedule finding,*** C [redacted] ***groups***
- ***Visit 2 (Day 31) and Visit 5 (Day 211) – Phase II, Formulation and Schedule finding, Control group***
- Visit 2 (Day 31) and Visit 3 (Day 61) – Phase II, Sourcing.

10.10.3. Protocol amendment 2

Detailed description of *current* Protocol amendment: *New text is shown in bold italics and deleted text is shown in strikethroughs.*

In the Title page:

Other study intervention(s)	**Phase I** • Placebo **Phase II** • GSK's meningococcal group B vaccine (*Bexsero*) • GSK's combined meningococcal groups A, C, Y and W-135 conjugate vaccine (*Menveo*) • ~~GSK's combined reduced antigen content diphtheria-tetanus toxoids and acellular pertussis vaccine (Tdap) (*Boostrix*)~~ • Placebo

Detailed title in Title page, Protocol Amendment 2 Sponsor Signatory Approval and Protocol Amendment 2 Investigator Agreement:

Title	A Phase I/II, ~~observer-blind,~~ randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II).

In Section 1.3, Schedule of activities (Table 1, Table 3 and Table 5):

Post-injection assessment (30 minutes)	(as per Table)	***See Section 10.3.8.1 for more information***

^ *Procedure to be performed prior to study intervention administration*

In Section 2.2, Background:

The Meningococcal Group B Vaccine (*Bexsero*) contains C [redacted]

C *Bexsero* is immunogenic against the majority of circulating meningococcal serogroup B strains and has acceptable reactogenicity and safety profiles when administered to individuals across age groups. The vaccine is currently approved in more than 40 countries worldwide. Although the meningococcal group B vaccine was developed for individuals aged 2 months and older, the actual age range for which this recommendation extends varies depending on the approval from different health authorities.

In Section 2.3, Benefit/Risk assessment:

Detailed information about the known and expected benefits and risks and expected adverse events of *Bexsero* (MenB)~~,~~ ***and*** *Menveo* (MenACWY) ~~and *Boostrix* (Tdap)~~ vaccine can be found in the Prescribing Information or Summary of Product Characteristics.

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 (as per the phase in which they are participating: Visit V1 and Visit V3 in Phase I, Visit V1, Visit V3 and Visit V4 in Phase II Formulation and Schedule-Finding and Visit V1 and Visit V2 in Phase II Sourcing). Refer to Section 6.1.

In terms of study procedures, blood sampling is associated with a risk of syncope, dizziness, local reactions and infection after or during venepuncture. For this reason, blood samples in this study will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the Informed Consent Form. ~~Appropriate medical treatment will be readily available.~~

In Section 3, Objectives and endpoints:

Note 1: MenB immune response will be assessed against *N. meningitidis* serogroup B indicator strains C

In Section 4.1.2.1, Phase II: Formulation and Schedule-finding:

Phase II (Formulation and Schedule-finding) will include 5 study groups, with a staggered enrolment (45 participants for safety lead-in and ~~840~~ ***955*** participants thereafter) of a total of ~~885~~ ***1000*** participants (Figure 2):

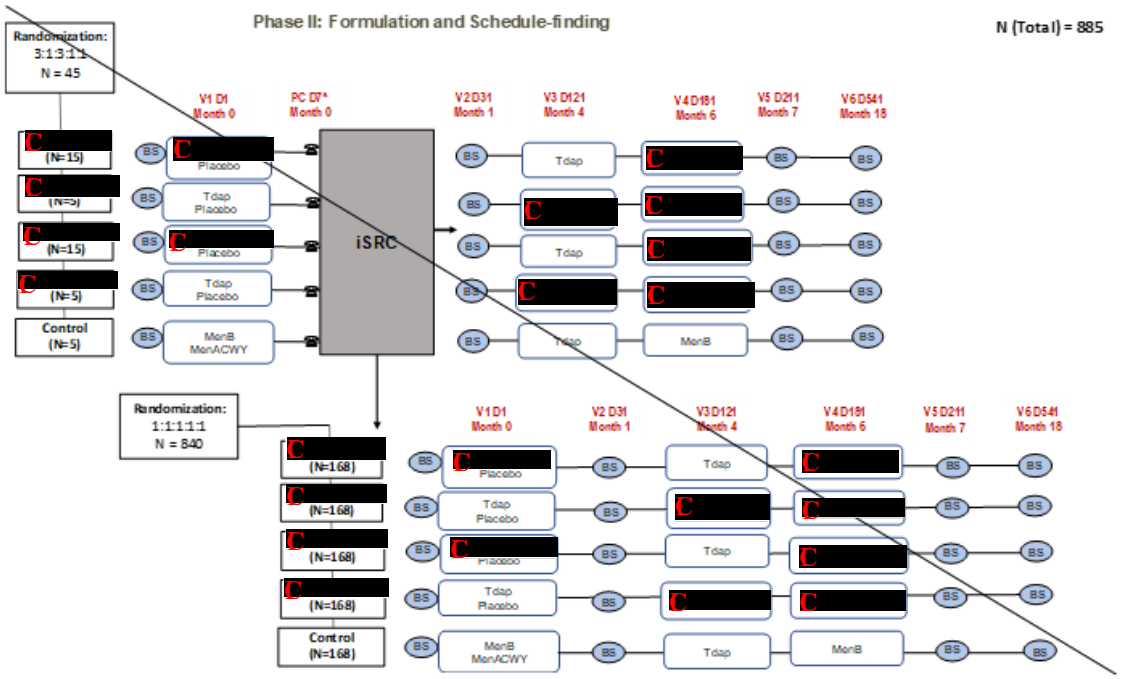
- C : Participants will receive 2 vaccinations of the C vaccine in a (0,6-months) schedule.
- C : Participants will receive 2 vaccinations of the C vaccine in a (0,2-months) schedule.
- C : Participants will receive 2 vaccinations of the C vaccine in a (0,6-months) schedule.
- C : Participants will receive 2 vaccinations of the C vaccine in a (0,2-months) schedule.

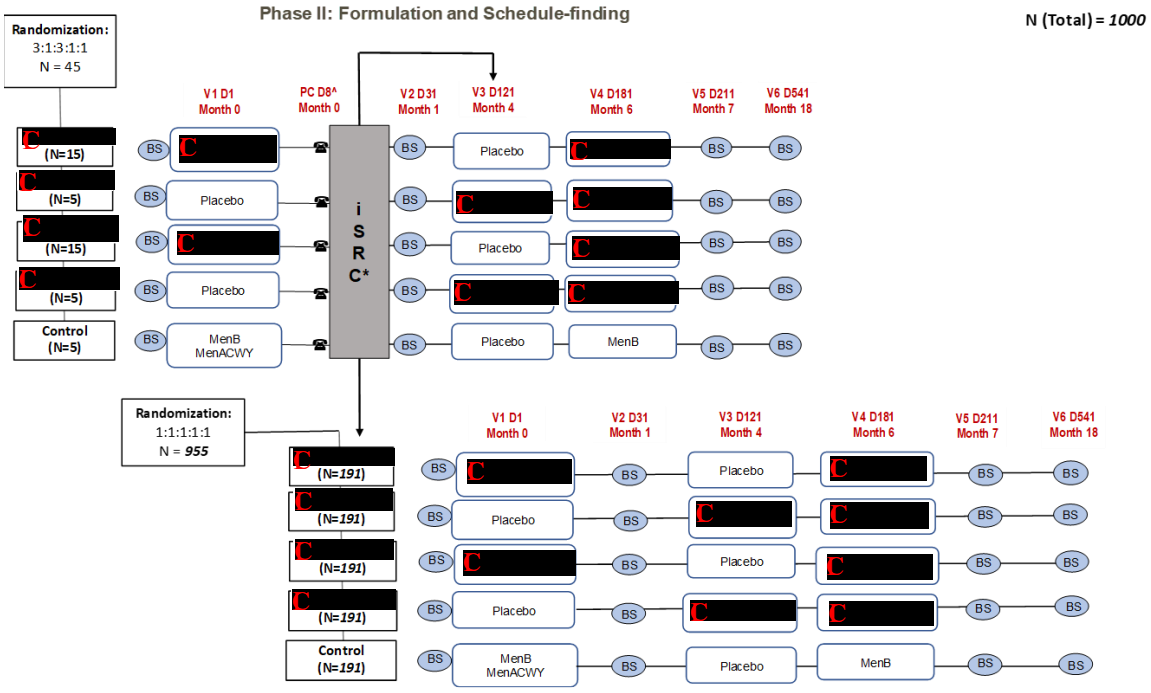
The above 4 groups will also receive 1 ~~vaccination each of the combined tetanus, diphtheria, and pertussis (Tdap, *Boostrix*) vaccine and~~ ***injection of*** placebo, according to the schedule described in *Figure 2*.

- **Control**: Participants will receive 2 vaccinations of MenB vaccine (*Bexsero*) in a (0,6-months) schedule and a single vaccination of MenACWY vaccine (*Menveo*). They will also receive 1 ~~vaccination of Tdap~~ ***injection of placebo***.

For more detailed information on study groups and treatments administered, Refer to Table 9 and Table 12.

The schedule of activities in Phase II (Formulation and Schedule-finding) of the study is described in Table 3.





Abbreviation: N, number of participants; V, clinic visit; D, day; iSRC, internal safety review committee; PC, phone contact; BS, blood sample.

^ The phone call at Day 8 is only for the first 45 participants (15 participants in C , 5 participants in C , 15 participants in C , 5 participants in C and 5 participants in the Control groups).

* The outcome of the iSRC will impact the next study intervention at Month 4. The Month 1 blood sampling will proceed as planned

Note 1: Blood draw at Visit 6 Month 18 will be used only for assessment of tertiary objectives.

Note 2: This figure represents the main aspects of the study design. Refer to Table 3, Schedule of activities, for details on all visits and contacts

Note 3: The Phase II (Formulation and Schedule-finding) is partially blinded. Study conduct and data collection in groups C will be observer-blind while in group Control it will be open-label.

Note ~~3~~ ***4***: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Refer to the SoA (Table 3) for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM. Refer to Section 8 (decentralised study procedures) for details

Note 4 ***5***: Refer to Section 8 for information on study procedures during special circumstances.

If the decision is "go", further vaccination at Month 4 and other study procedures following that will continue in these groups along with continuing to recruit participants with a randomisation ratio of 1:1:1:1:1 (~~168~~ ***191*** in each group) to reach the target total sample of ~~840~~ ***955*** participants. Refer to Table 9 for total number of participants per group.

Table 9 Study groups, intervention and blinding – Phase II (Formulation and Schedule-finding)

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
C	~~183~~ ***206***	10 – 25 yoa	C ~~Tdap~~ NaCl	Observer-blinded
	~~173~~ ***196***	10 – 25 yoa	C ~~Tdap~~ NaCl	
	~~183~~ ***206***	10 – 25 yoa	C ~~Tdap~~ NaCl	
	~~173~~ ***196***	10 – 25 yoa	C ~~Tdap~~ NaCl	
Control	~~173~~ ***196***	10 – 25 yoa	MenACWY rMenB+OMV NZ ~~Tdap~~ ***NaCl***	~~Observer-blinded~~ ***Open-label***

In Section 4.1.2.1, Phase II: Sourcing:

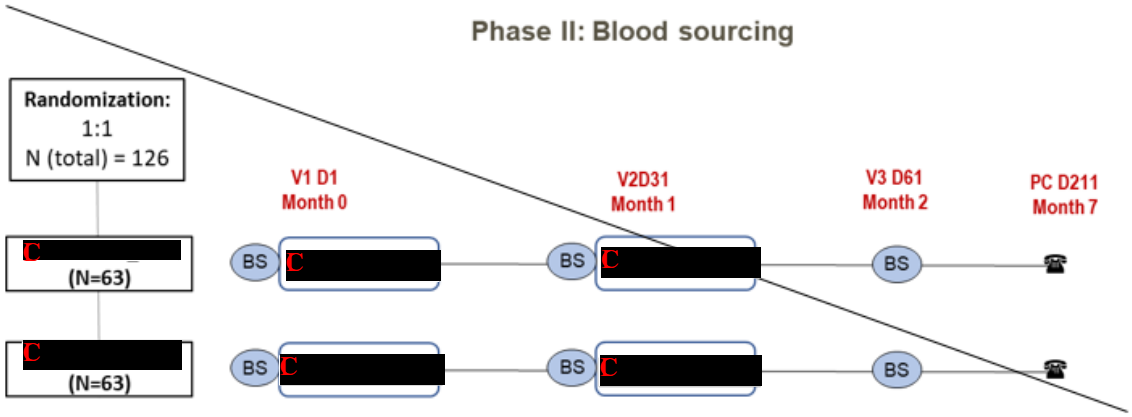
The blood sourcing part of the Phase II study will include 2 groups (randomised 1:1), with a parallel enrolment of a total of ~~126~~ ***226*** participants (*Figure 3*):

- C : Participants will receive 2 vaccinations of the C vaccine in a (0,1-month) schedule.
- C : Participants will receive 2 vaccinations of the C vaccine in a (0,1-month) schedule.

For more detailed information on study groups and treatments administered, Refer to Table 10 and Table 13.

The schedule of activities in the Phase II (sourcing) is described in Table 5.

Figure 3 Study design overview – Phase II (Sourcing)



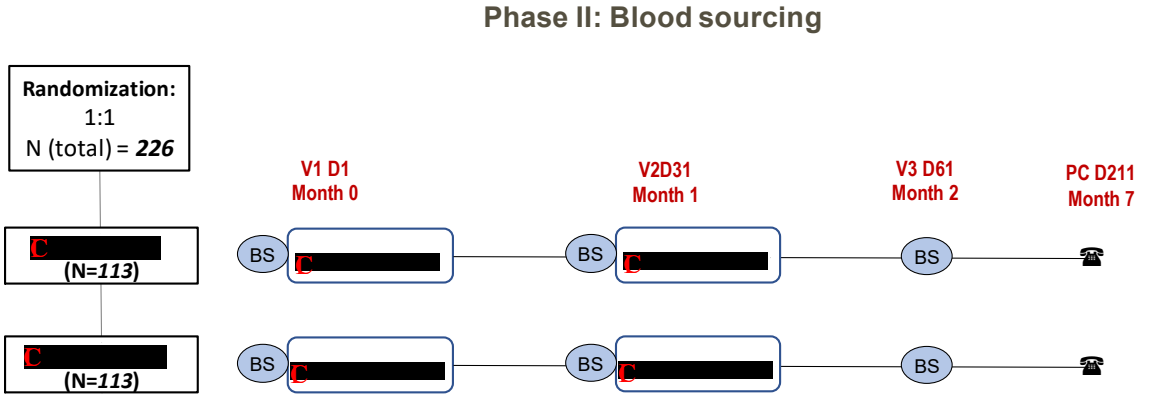


Table 10 Study groups, intervention and blinding – Phase II (Sourcing)

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
C	~~63~~ ***113***	18-~~40~~ ***50*** yoa	C	Observer-blinded
C	~~63~~ ***113***	18-~~40~~ ***50*** yoa	C	

In Section 4.2, Scientific rationale for study design:

~~The Tdap vaccine is indicated for the booster immunisation against tetanus, diphtheria and pertussis as a single dose in individuals 10 years of age and older. It is a non-investigational study vaccine, administered to maintain the blinding of the Phase II of the study (along with placebo).~~

In Section 5.1, Inclusion criteria:

- **Phase I ~~and Phase II (Sourcing)~~ only**: A male or female between, and including, 18 and 40 years of age (i.e. 40 years + 364 days) at the time of the first study intervention administration.
- ***Phase II (Sourcing) only: A male or female between, and including, 18 and 50 years of age (i.e. 50 years + 364 days) at the time of the first study intervention administration.***
- ~~**Phase II (Formulation and Schedule-finding) only**: Participants who have received previous doses of tetanus, diphtheria, and pertussis vaccine can participate in the study if they have received it at least 5 years prior to informed consent (and assent, as applicable).~~

In Section 5.2 Exclusion criteria, in Section 5.2.1, Medical conditions:

- Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 3 months prior to study vaccination until the last blood sampling visit for Phase I and Phase II (Sourcing) and Visit 5 (Day 211) for Phase II (Formulation and Schedule-finding). ~~This will mean for adult participants prednisone or equivalent ≥20 mg/day, and for paediatric participants ≥0.5 mg/kg/day or ≥20 mg/day, whichever is the maximum dose~~. ***This will mean prednisone equivalent ≥20 mg/day***

for adult participants/ ≥0.5 mg/kg/day with maximum of 20 mg/day for paediatric participants. Inhaled and topical steroids are allowed.

In Section 5.2 Exclusion criteria, in Section 5.2.2, Prior/Concomitant therapy:

- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose(s) until the last blood sampling visit for Phase I and Phase II (Sourcing) and Visit 5 (Day 211) for Phase II (Formulation and Schedule-finding). For corticosteroids, this will mean ~~for adult participants prednisone or equivalent ≥20 mg/day, and for paediatric participants ≥0.5 mg/kg/day or ≥20 mg/day, whichever is the maximum dose~~ ***prednisone equivalent ≥20 mg/day for adult participants/ ≥0.5 mg/kg/day with maximum of 20 mg/day for paediatric participants***. Inhaled and topical steroids are allowed.

In Section 5.5, Criteria for temporarily delaying enrolment/ randomisation/ study intervention administration/blood sampling:

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

In Section 6.1, Study intervention(s) administered:

Table 11 Study intervention administered – Phase I

Study intervention name:	C [redacted]		**Placebo**
~~**Type**~~	~~Biologic product~~	~~Biologic product~~	~~Not applicable~~
Product category	***Combination***	***Combination***	***Combination***
Type ~~of intervention~~	Study	Study	Control

Table 12 Study intervention administered – Phase II (Formulation and Schedule-finding)

Study intervention	[redacted]	*Bexsero*	*Menveo**	~~*Boostrix (Ex-US formulation)*~~[3]	~~*Boostrix (US formulation)*~~[3]	Placebo (saline)
Formulation†	[redacted]					Sodium chloride (NaCl) (0.9%); Water for injections

Study intervention	C		***Bexsero***	***Menveo****	~~***Boostrix (Ex-US formulation)***~~[3]	~~***Boostrix (US formulation)***~~[3]	**Placebo (saline)**
	C						
Dose Form/ Presentation							Solution for injection/ Syringe
~~**Type**~~	~~Biologic product~~	~~Biologic product~~	~~Biologic product~~	~~Biologic product~~	~~Biologic product~~		~~Not applicable~~
Product category	***Combination***	***Combination***	***Combination***	***Biological***			***Combination***
No of doses							
C	2	-	-	-	~~1~~		1
	2	-	-	-	~~1~~		1
	-	2	-	-	~~1~~		1
	-	2	-	-	~~1~~		1
Control	-		2	1	~~1~~		~~***1***~~
Volume to be administered^	CCI						
Type ~~of interve~~	Study	Study	Control	Control	~~Concomitant~~		Concomitant

Study intervention	C		***Bexsero***	***Menveo****	~~***Boostrix (Ex-US formulation)***~~[3]	~~***Boostrix (US formulation)***~~[3]	**Placebo (saline)**
~~**ntion**~~							
Route of administration	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use	~~Intramuscular use~~		Intramuscular use
Administration site							
Location	Deltoid	Deltoid	Deltoid	Deltoid	~~Deltoid~~		Deltoid
Laterality***	Non-dominant***	Non-dominant***	Non-dominant***	Dominant	~~Non-dominant***~~		~~Dominant~~ ***Non-dominant***
Packaging, labelling and TM:	Refer to SPM for details						
Manufacturer:	GSK	GSK	GSK	GSK	~~GSK~~		GSK

~~[3] The US formulation of *Boostrix* will be administered to participants included in the study in US. In all other countries, participants will receive the ex-US formulation of the same vaccine~~

*** (Not for Visit 1 ***in Control group***) The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed

Table 13 Study intervention administered – Phase II (Sourcing)

Study intervention name:	C	
~~**Type**~~	~~Biologic product~~	~~Biologic product~~
Product category	***Combination***	***Combination***
Type ~~of intervention~~	Study	Study

In Section 6.3.2, Randomisation to study intervention:

There are 2 randomisation processes for each participant in the study:

- Randomisation to study intervention
- C

In Section 6.3.3, Intervention allocation to the participant:

It is recommended to have a balance between age category during enrolment in Phase II (Formulation and Schedule-finding).

In Section 6.3.4, Allocation of participants to assay subsets:

Refer to Section 9 for details on the allocation as per the MenACWY priming and the analysis planned. Blood samples will be collected as detailed in Section 8.1.1.1. Refer to Section 10.2.1 for details on allocation of participants for safety laboratory assays.

Refer to Section 8.1.3 for details on allocation of participants to assay subsets ***and*** C

Note: The following section has only been moved from 6.3.4 to 10.2.2.1.1 therefore not presented as new text.

In Section 6.3.5, Blinding and unblinding:

6.3.5.1 Phase I and Phase II (Sourcing)

Data will be collected in an observer-blind manner. To do so, study intervention(s) will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety, efficacy).

The 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 and the identity of the participant.

6.3.5.2 Phase II (Formulation and Schedule-finding)

This phase is partially blinded. Data in the 4 ABCWY groups will be collected in an observer-blind manner. To do so, study intervention(s) will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety,

efficacy). Data in the Control group will be collected in an open-label manner i.e. study participants, investigator and site staff personnel will be aware of the treatment administered as 2 study interventions are administered at Visit V1.

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

Refer to the SPM for additional information about details on study blinding.

In Section 8.1.1.1, Blood sample:

Table 20 Blood samples at Phase II (Formulation and schedule-finding)

Sample type	Quantity	Unit	Timepoint	Subset name/ Group	Day
Blood	***Approximately*** 15	mL	Visit V1 (*)	All participants	Day 1
Blood	***Approximately*** 15	mL	Visit V2 (**)	All participants	Day 31
Blood	***Approximately*** 30	mL	Visit V5 (Post-Vacc 2)	All participants	Day 211
Blood	***Approximately*** 30	mL	Visit V6 (^)	All participants	Day 541

In Section 8.1.2, Laboratory assays:

Table 21 Laboratory assays – Phase I and II

CCI

CCI [redacted]

CCI [redacted]

In Section 8.2.1.1, Collection of demographic data:

For Phase II (Formulation and Schedule-finding) only: At Visit V1 ***in the Control group,*** the participant receives 2 injections, one in either arm. Therefore, in order to associate the solicited events reported to the vaccine administered in that arm, the dominant arm (left or right) will be recorded in the eCRF (Table 12).

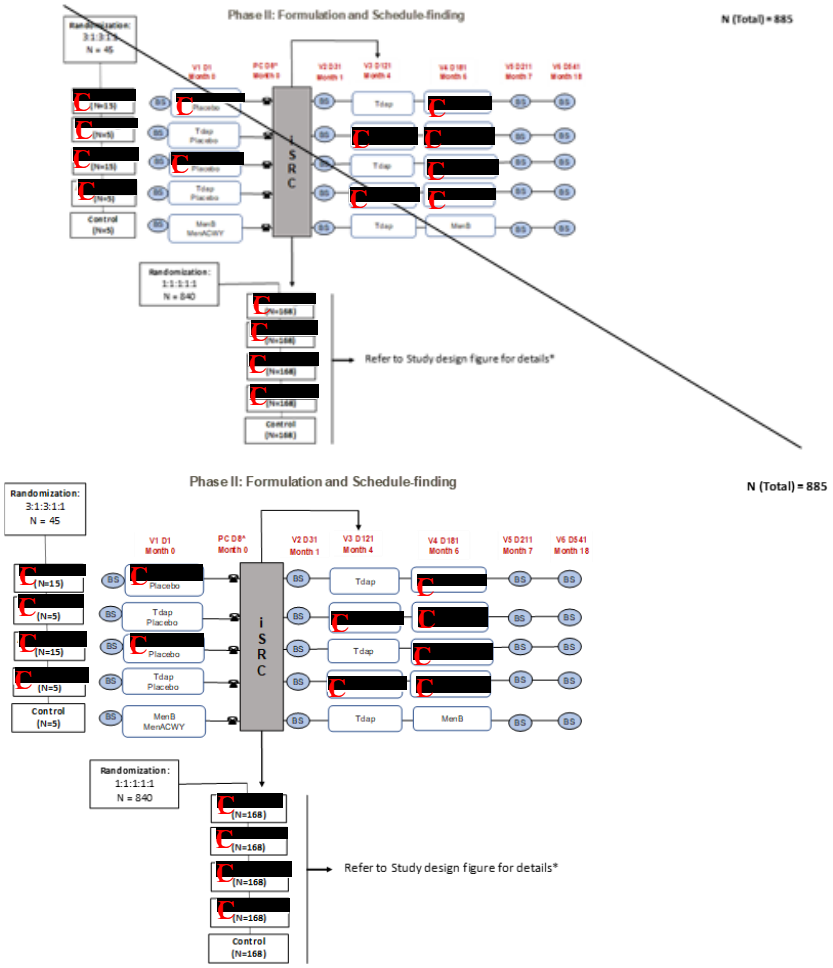
In Section 8.2.1.5, Warnings and precautions to vaccination:

Refer to the approved product label/package insert of Bexsero ***and*** Menveo. ~~and *Boostrix.*~~

In Section 8.2.2.1, Safety data review:

Step 3: Following the second vaccination in CCI [redacted] groups at Day ~~30~~ ***31***, all available safety data from all participants collected up to Day 38 will be evaluated by the iSRC.

Figure 5 Step-wise approach for safety review in Phase II (Formulation and Schedule-finding)



Phase II: Formulation and Schedule-finding
N (Total) = 885
Randomization: 3:1:3:1:1 N = 45
V1 D1 Month 0
PC D8* Month 0
V2 D31 Month 1
V3 D121 Month 4
V4 D181 Month 6
V5 D211 Month 7
V6 D541 Month 18
BS
Placebo
Tdap
Tdap Placebo
MenB MenACWY
Control (N=5)
iSRC
Randomization: 1:1:1:1:1 N = 840
(N=168)
Refer to Study design figure for details*

If the decision is "go", the enrolment in all groups will continue with a randomisation ratio of 1:1:1:1:1 to the target total sample of ~~885~~ ***1000*** participants and the administration of the second vaccination at Month 4 will take place in the 45 participants as per their group allocation.

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

In Section 8.2.2.1.2, Outcome of safety evaluation

If a safety signal is observed during the safety evaluations or if any of the holding rules 2a-c is met (Table 25), the iSRC Chair (or his/her representative) is responsible for the urgent communication ~~to~~ within GSK, including the rationale for the decision to put the study intervention administration on hold or not.

In Section 8.2.2.1.3, Study holding rules:

Table 26 Study holding rules – Phase II (Formulation and Schedule-finding)

Holding rule	Event	Number or % of participants needed to trigger the hold
1a	Death or any life-threatening **SAE** regardless of causality	≥ 1
2a	Any **Grade 3 solicited administration site event** (lasting 48h or more) in the investigational group, with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 20%
2b	Any **Grade 3 solicited systemic event** (lasting 48h or more) in an investigational group, with an event onset within the 7-day (Day 1-7) post-injection period	≥ 20%
2c	Any **Grade 3 unsolicited AE** in an investigational group, that can be reasonably attributed to the vaccination, with an event onset within the 7-day (Day 1-7) post-injection period	≥ 20%

Abbreviations: AE, adverse event; SAE, serious adverse event~~; TBD, To be determined.~~

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

Table 27 Timeframes for collecting and reporting of safety information – Phase I

Event	On V1*	V1	~~V2~~	V3	~~PC~~	V4	PC	Phase I conclusion
		D1***	D7	D31	D37	D61	D151	D 211 (PC)

In Section 8.3.3,

Table 30 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	~~2 weeks~~ ***24 hours****	electronic pregnancy report	~~2 weeks~~ ***24 hours****	electronic pregnancy report
AESIs	24 hours**, ‡‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

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

In Section 8.3.4, Treatment of adverse events:

Any medication administered for the treatment of an SAE/AESI should be recorded in the ~~Expedited Adverse Event Report of the participant's~~ eCRF ~~screen~~ (refer to the Section 10.3.10.1).

Section 8.3.6, Medical device deficiencies has been added:

Section 8.3.6 Medical device deficiencies

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

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

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

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.7 for definitions and details on recording and reporting of these events.

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

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

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

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to section 10.7.3 for details of reporting.

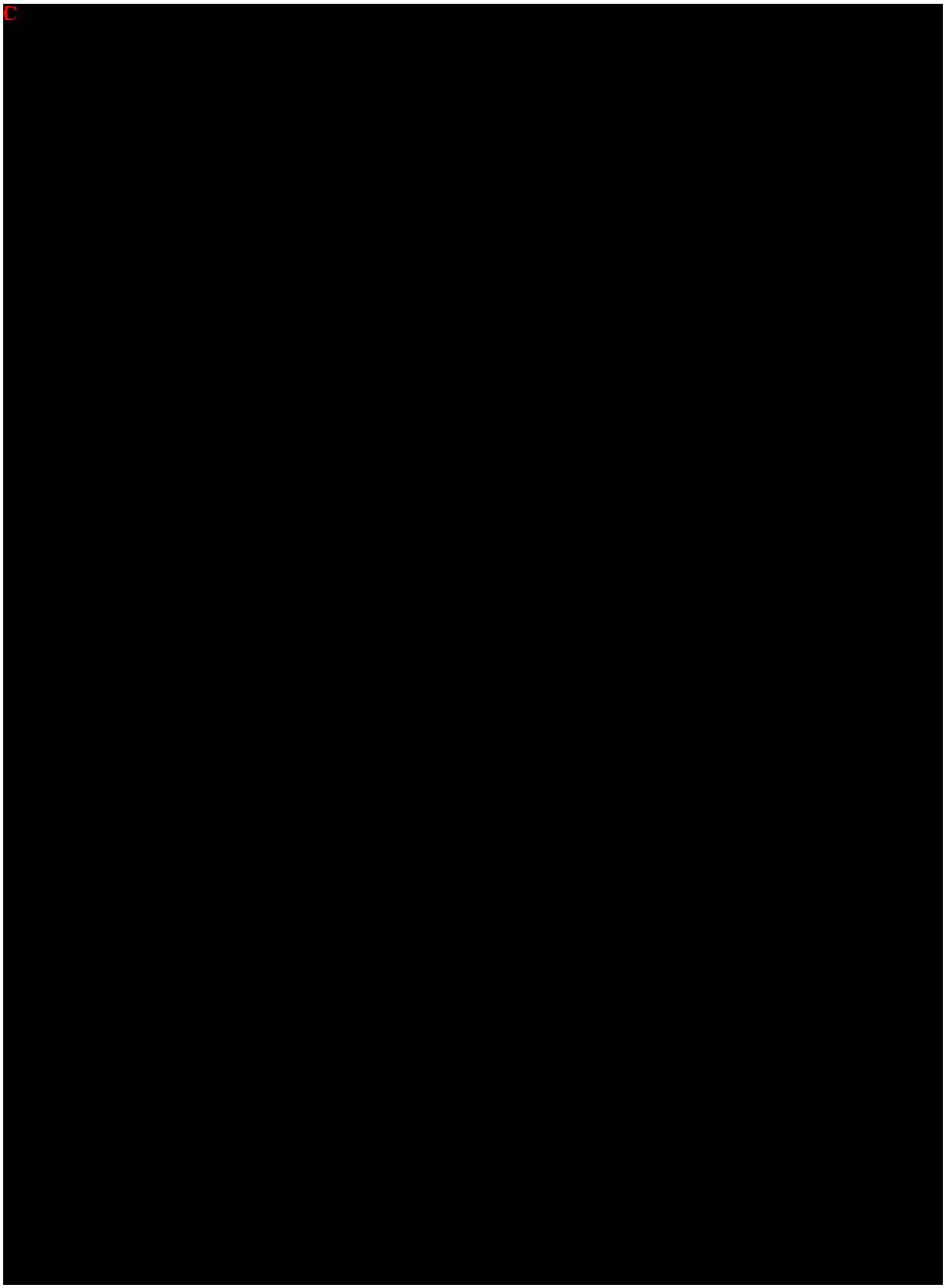
The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

In Section 9.2, Sample size determination, 9.2.2, Phase II (Formulation and Schedule-finding):

~~Eight hundred and eighty-five (885)~~ ***A thousand (1000)*** participants are to be enrolled in 5 arms of Phase II of the study, ~~183~~ ***206*** participants for both C arms and ~~173~~ ***196*** participants for C and Control arms. It is assumed that 15% of the participants will drop out or will not contribute to an evaluable result for the primary endpoints resulting in about ~~150~~ ***170*** evaluable participants per arm.

In Section 9.2.2.1, Superiority of vaccine effectiveness of the CCI vaccine (CCI) when administered at 0,2- or 0,6-m schedule compared to the Control vaccine (MenB)

C



C [redacted]

In Section 9.2.3, Phase II (Sourcing):

~~One~~ ***Two*** hundred and twenty-six (~~126~~ ***226)*** participants are to be enrolled in 2 arms of Phase II (Sourcing) of the study, ~~63~~ ***113*** participants each in C [redacted] group (1:1 randomisation).

In Section 9.4.2, Primary endpoint(s) – Phase II (Formulation and Schedule-finding):

Primary Endpoint	Statistical Analysis Methods
Superiority of effectiveness	C [redacted]

In Section 9.4.4, Secondary endpoint(s) – Phase II (Formulation and Schedule-finding):

Secondary Endpoint	Statistical Analysis Methods
Description of the distribution of B strains killed	CCI [redacted]
Immune response to *serogroup* B *indicator* strains	[redacted]
Immune response to *serogroups* A,C,W and Y ~~serogroups~~	[redacted]

Secondary Endpoint	Statistical Analysis Methods
	CCI [redacted]

CCI [redacted]

Tertiary Endpoint	Statistical Analysis Methods
CCI [redacted]	

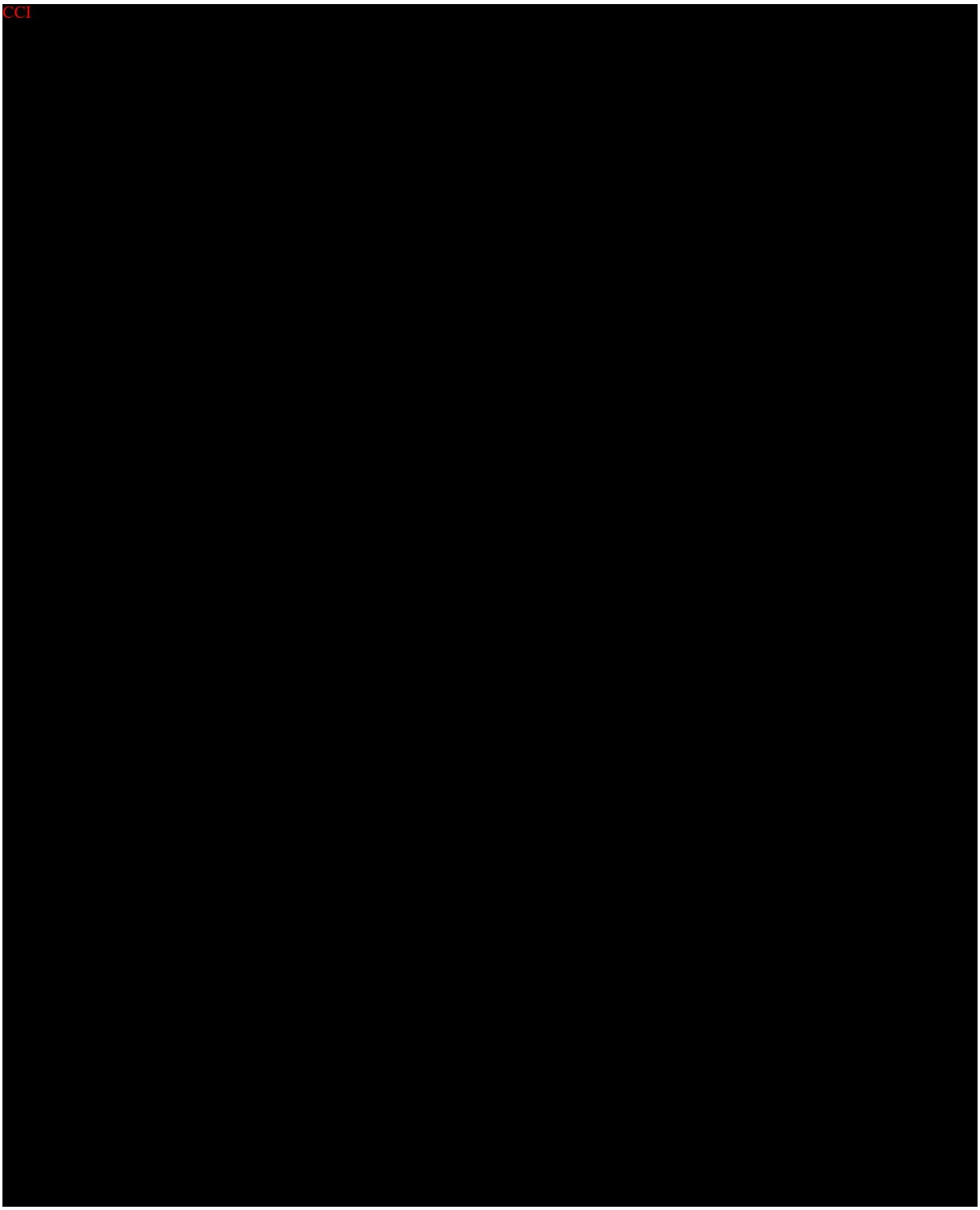
CCI [redacted]

In Section 10.1.4, Data protection:

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

The bullet format has been removed for the above as it is an independent statement.

CCI



In Section 10.3.8.1, Time period for collecting and recording AEs, SAEs, AESIs and pregnancies:

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

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

In Section 10.3.9.3, Medically attended visits:

For each solicited and unsolicited AE the participant experiences ***(Refer to Table 27, Table 28 and Table 29)***, the participant/participant's parent(s)/LAR(s) will be asked if he/she/the participant received medical attention (defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the eDiary/ eCRF.

In Section 10.3.10.1, Events requiring expedited reporting to GSK:

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

Added:

Section 10.7, Appendix 7: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

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

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

10.7.2 Definition of medical device SAE, SADE and USADE

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

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

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

- ***Contacts for reporting can be found in Section 8.3.3.1.***

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

In Section 10.9.1, List of abbreviations

ADE:	***Adverse Device Effect***
SADE:	***Serious Adverse Device Effect***
USADE	***Unanticipated Serious Adverse Device Effect***

In Section 10.9.2, Glossary of terms

Blinding:	A procedure in which 1 or more parties to the trial 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 trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. ***For Phase I and Phase II Sourcing:*** In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. ***For Phase II Formulation and Schedule-finding: Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group.***
Medical device deficiency:	***A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.***

10.10.4. Protocol amendment 1

Detailed description of the Protocol amendment (Amendment 1): This is a country-specific protocol amendment pertaining to Phase 1 part (conducted in Australia) of this seamless Phase I/II study. The blood tubes which are required for collection of blood samples for safety laboratory evaluation in Phase 1 hold a maximum volume of 7 mL and it is not possible to measure 6 mL volume in these tubes. Therefore in order to avoid the risk of collecting lower volume of blood, this protocol has been amended to document the change in the blood sample volume for the safety laboratory evaluation (from 6 mL to 7 mL).

New text is shown in bold italics and deleted text is shown in strikethroughs.

In Section 1.3, Schedule of Activities, under Table 1 Schedule of Activities – Phase I

Table 1 Schedule of Activities – Phase I

Type of contact	Visit	Visit	Visit	PC	Visit	PC	PC	Notes
Visit/Phone call no.	V1	V2	V3	T1	V4	T2	T3	
Timepoint(s) [refer to Table 2 for visit windows]	Day 1	Day 8	Day 31	Day 38	Day 61	Day 151	Day 211	
Blood sampling for safety laboratory evaluation	•	•						Blood volume of ~~6~~ ~7 mL will be collected. See Section 8.1.1.1 for more information

In Section 8.1.1.1, Blood Sample:

Phase I: An overall blood volume of 240 mL per participant will be collected over the course of the Phase I part of the study. An additional ~~6~~ *7* mL of blood will be collected at Visit V1 and Visit V2 from all participants for the safety laboratory evaluation. Refer to Table 18 for details.

Table 18 Blood samples at Phase I

Sample type	Quantity	Unit	Timepoint	Subset name/ Group	Day
Blood	Approximately 80	mL	Visit V1 CCI ;	All participants	Day 1
Blood	Approximately 80	mL	Visit V3 (CCI	All participants	Day 31
Blood	Approximately 80	mL	Visit V4 (CCI	All participants	Day 61
Blood	Approximately ~~6~~ **7**	mL	Visit V1	All participants	Day 1
Blood	Approximately ~~6~~ **7**	mL	Visit V2	All participants	Day 8

Pre-Vacc, Pre-vaccination timepoint; Post-Vacc, Post-vaccination timepoint

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