CLINICAL STUDY PROTOCOL
SPONSOR:
GlaxoSmithKline Biologicals SA (GSK)

Primary study intervention	GSK's mRNA Clinical Research CR-04
Other study intervention	Placebo (normal saline)
Study identifier	219112 (MRNA CLINRES-001)
NCT identifier number	NCT05972993
IND number	29606
Date of protocol	Final: 11 May 2023
Date of protocol amendment	Amendment 3 Final: 07 Feb 2024
Title	Exploratory, FTIH, observer-blind, randomized, controlled study to evaluate safety, reactogenicity and immunogenicity of various doses of GSK's investigational mRNA-CR-04 vaccine when administered intramuscularly in healthy adults 18 to 49 years of age
Brief title	A safety and immune response study to evaluate varying doses of an mRNA vaccine against COVID-19 in healthy adults
Sponsor signatory	Pavitra Keshavan, Sr. Director, Clinical Project Lead, Vaccines Clinical Sciences

Based on GSK Protocol WS v17.3

PROTOCOL AMENDMENT 3 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 GSK and/or CRO.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- 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 study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-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.
- 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 study.
- 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 their 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	219112 (MRNA CLINRES-001)
NCT identifier number	NCT05972993
IND number	29606
Date of protocol	Final: 11 May 2023
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Title	Exploratory, FTIH, observer-blind, randomized, controlled study to evaluate safety, reactogenicity and immunogenicity of various doses of GSK's investigational mRNA-CR-04 vaccine when administered intramuscularly in healthy adults 18 to 49 years of age
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GSK (Rixensart)

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 SAEs

Back up study contact for reporting SAEs: refer to Section 8.4.7.

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

5. Emergency unblinding

Refer to Section 6.3.4.

PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Date	Substantial	Region
Amendment 3	07 Feb 2024	Yes	United States (US)
Amendment 2	15 Nov 2023	Yes	United States (US)
Amendment 1	03 Oct 2023	Yes	United States (US)
Original Protocol	11 May 2023	-	-

Overall Rationale for the Amendment:

The Protocol Amendment 3 has been amended to allow for additional Day 31 interim analyses and to add a Part B to the study following the Day 15 interim analysis, during which a lower dose (3 µg) of the mRNA-CR-04 vaccine will be evaluated and sponsor personnel will be unblinded.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 (Synopsis), Section 1.2 (Schema), Section 4.1 (Overall design), Section 4.2 (Scientific rationale for study design), Section 4.3 (Justification for dose), and Section 6.3.3 (Intervention allocation to the participant).	This study is divided into two parts (Parts A and B). Part B will commence only after all Part A participants have completed their Day 15 study visits and the Day 15 interim analysis is completed. In Part B, 42 more participants will be enrolled in parallel and randomly assigned in a 3:3:1 ratio to receive: (a) 3 µg mRNA-CR-04 vaccine, or (b) 10 µg mRNA-CR-04 vaccine, or (c) saline placebo.	To explore a wider range of vaccine doses and to repeat the 10 µg dose vaccine group, which may assist in standardizing the Part B to Part A study groups.
Section 1.1 (Synopsis), Section 1.2 (Schema), Section 4.1 (Overall design), Section 6.3.4 (Blinding and unblinding), Section 8.3.7.1 (Staggered administration of study intervention), Section 8.3.7.4 (SRT and iSRC evaluation), and Section 8.4.4.2.1 (Myocarditis and pericarditis: definitions and assessment).	Text modified to allow unblinding of sponsor personnel (including the SRT) to individual level treatment assignments following the Part A Day 15 interim analysis. The observer-blind will be maintained at the site level.	Practical consideration to allow all sponsor personnel to use unblinded data analyses from this initial phase 1 trial to plan further clinical development of the investigational vaccine platform. The SRT will no longer need to rely on the iSRC as the sole reviewer of unblinded safety data.
Section 2.2 (Background) and Section 4.3 (Justification for dose).	FDA authorization of monovalent COVID-19 vaccine boosters encoding XBB.1.5 since 11 September 2023 added to text.	Since the prior protocol amendment, the FDA has approved and authorized new monovalent COVID-19 vaccines encoding this variant for administration as booster doses.
Section 6.1 (Study interventions administered).	Added a new table to specify the study interventions to be administered to Part B study participants.	To align with the new interventions planned for Part B of the study.
Section 8.2.3 (Immunological read-outs).	Revised the number of participants column to add the planned 42 Part B study participants.	To align with the planned additional study participants in Part B of the study.
Section 9.3 (Analysis sets).	Modified the per protocol analysis set definition to clarify the immunogenicity endpoint of interest	To align the per protocol set definition immunogenicity endpoint of interest with the endpoint

Section # and Name	Description of Change	Brief Rationale
	being the neutralizing antibody titer against pseudovirus bearing S protein and removed the overall safety analysis set.	specified in the statistical analysis plan and to remove the redundant overall safety analysis set.
Section 9.4.1 (Primary endpoint), Section 9.4.2.1 (Safety endpoints), Section 9.4.2.2 (Immunogenicity endpoints), and Section 9.4.3 (Analyses of exploratory immunogenicity endpoints).	Clarified that these statistical analyses will be performed descriptively and separately for study Part A and Part B participants and will be pooled for model based analyses.	To align with the additional analyses required with the addition of the study Part B participants.
Section 9.5.1 (Sequence of analyses).	Added text to perform a Day 31 interim analysis on Part A participants and to allow for potential Day 15 and Day 31 interim analyses for Part B participants.	To explicitly note the known and potential additional interim analyses currently planned for this study.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore not summarized.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
CFR	Code of federal regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLS	Clinical laboratory sciences
CoP	Correlate of protection
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSL	Clinical science lead
CSR	Clinical study report
ECL	Electro-chemiluminescence assay
ECMO	Extracorporeal membrane oxygenation
eCRF	electronic Case report form
EKG	Electrocardiogram
EMA	European Medicines Agency
EoS	End-of-study
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen

FSFV	First subject first visit
FSH	Follicle stimulating hormone
FTIH	First time in human
GCP	Good clinical practice
GMC	Geometric mean concentration
GMR	Geometric mean ratio
GMT	Geometric mean titer
GSB	Global safety board
GSK	GlaxoSmithKline Biologicals SA
hCG	human Chorionic gonadotropin
HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICS	Intracellular cytokine staining
IEC	Independent ethics committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
iSRC	Internal safety review committee

IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LNP	Lipid nano particles
LSLV	Last subject last visit
MAAE	Medically attended adverse event
MedDRA	Medical dictionary for regulatory activities
mRNA-CR vaccine	SARS-CoV-2 Omicron variant S glycoprotein vaccine
N	Nucleocapsid
NCT	National Clinical Trial
PaO_2	Partial pressure of oxygen
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PI	Personal information
pIMD	Potential immune-mediated disease
PM	Pharmacy manual
PP	Per Protocol
PPD	Pharmaceutical Product Development
PPS	Per Protocol Set
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
QTL	Quality tolerance limit
RNASeq	RNA sequencing
RT-PCR	Real-time polymerase chain reaction
S	Spike
SAE	Serious adverse event

SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of activities
SOC	System organ class
SpO_2	Pulse oximetry
SRT	Safety review team
TC	Telephone call
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-child-bearing potential
WT	SARS-CoV2 Wuhan ancestral strain or Wild type strain

Adverse Drug Reaction: An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition).

b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized

Adverse Event (AE): 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 AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Auxiliary Medicinal Product (AxMP): Medicinal products used in the context of a clinical trial but not as investigational medicinal products, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.

a. Authorized AxMP: Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product.

Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.

b. Unauthorized AxMP:	Medicinal product not authorized in accordance with Regulation (EC) No 726/2004. Safety reporting for unauthorized auxiliary medicinal products will follow the same processes and procedures as SUSAR safety reporting
Background treatment:	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious Aes 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.
Challenge agents:	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.
Co-administered (concomitant) products:	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator:	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).

eDiary:	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
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 studies.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological CoP:	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 Product:	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigational vaccine:	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: IMP

Investigator:	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Medicinal products used to assess end-points:	A product given to the participant in a Clinical Trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
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.
Placebo:	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Rescue medication:	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Standard of Care:	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Study monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR:	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.
Telemedicine:	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, patient and professional health-related education, public health and health administration.
Unsolicited AE:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited AE.

1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale: GSK is developing a novel mRNA vaccine platform where the SARS-CoV-2 Omicron variant S glycoprotein will be used as an antigen model (hereafter referred to as mRNA-CR vaccines). This mRNA vaccine platform development includes several mRNA constructs (mRNA-CR-XX) currently under development that will be progressing into clinical research in humans.

Objectives, endpoints and estimands: This exploratory, FTIH study is to evaluate the safety, reactogenicity and immune responses of the mRNA-CR-04 vaccine construct when administered in healthy adults previously vaccinated with SARS-CoV-2 mRNA vaccines. For details on objectives, endpoints and estimands, refer to Section 3.

Overall design: This will be a Phase 1, observer-blind, randomized, placebo-controlled, multicenter, dose-escalation study evaluating in Part A of the study, 3 doses (10 µg, 30 µg, and 100 µg) of the mRNA-CR-04 (Omicron BA.5 strain) vaccine. Approximately 72 participants will be enrolled with 24 participants per group (Group 1, Group 2 and Group 3). Within each group, participants will be randomly assigned in a 3:1 ratio to receive:

- investigational mRNA-CR-04 vaccine (SPK001-AC01 mRNA-LNP) or
- saline placebo.

For each group, 8 sentinel participants will first be enrolled and vaccinated. Enrollment of participants in Group 1 and Group 2 will be done in parallel with the first participant to be enrolled in Group 1. Only if no safety signal is observed, vaccination of the non-sentinel participants in that group will continue. If no safety signals observed in sentinel participant in Group 1 and Group 2, enrollment, and vaccination of the sentinel participants in Group 3 will be initiated. Refer to Section 4.1 and Figure 1 for more details on the study design.

Part B of the study will commence only after all Part A participants have completed their Day 15 study visits and the Day 15 interim analysis is completed. In Part B, 2 doses (3 µg and 10 µg) of the mRNA-CR-04 (Omicron BA.5 strain) vaccine will be evaluated. Approximately 42 participants will be enrolled in parallel in Part B and there will be no sentinel participants. Part B participants will be randomly assigned in a 3:3:1 ratio to receive:

- 3 µg investigational mRNA-CR-04 vaccine (SPK001-AC01 mRNA-LNP) or
- 10 µg investigational mRNA-CR-04 vaccine (SPK001-AC01 mRNA-LNP) or
- saline placebo.

Data Monitoring/Other committees: Safety monitoring and safety data review will be performed by a GSK SRT (blinded data review until Part A Day 15 interim analysis, unblinded data review subsequently) and a GSK iSRC (unblinded data review). Safety holding rules and safety monitoring are presented in Section 8.3.7.

1.2. Schema

This is an exploratory, FTIH, observer-blind, randomized, multicenter, controlled study.

In Part A of the study, three doses (10 µg, 30 µg, and 100 µg) of the mRNA-CR-04 vaccine will be evaluated. Approximately 72 eligible healthy adults, 18 to 49 years, inclusive, will be enrolled with 24 participants per group (Group 1, Group 2 and Group 3). Within each group, participants will be randomly assigned in a 3:1 ratio:

- 18 participants will receive the investigational mRNA-CR-04 vaccine and
- 6 participants will receive a saline placebo (sodium chloride [NaCl] isotonic solution [0.9%]).

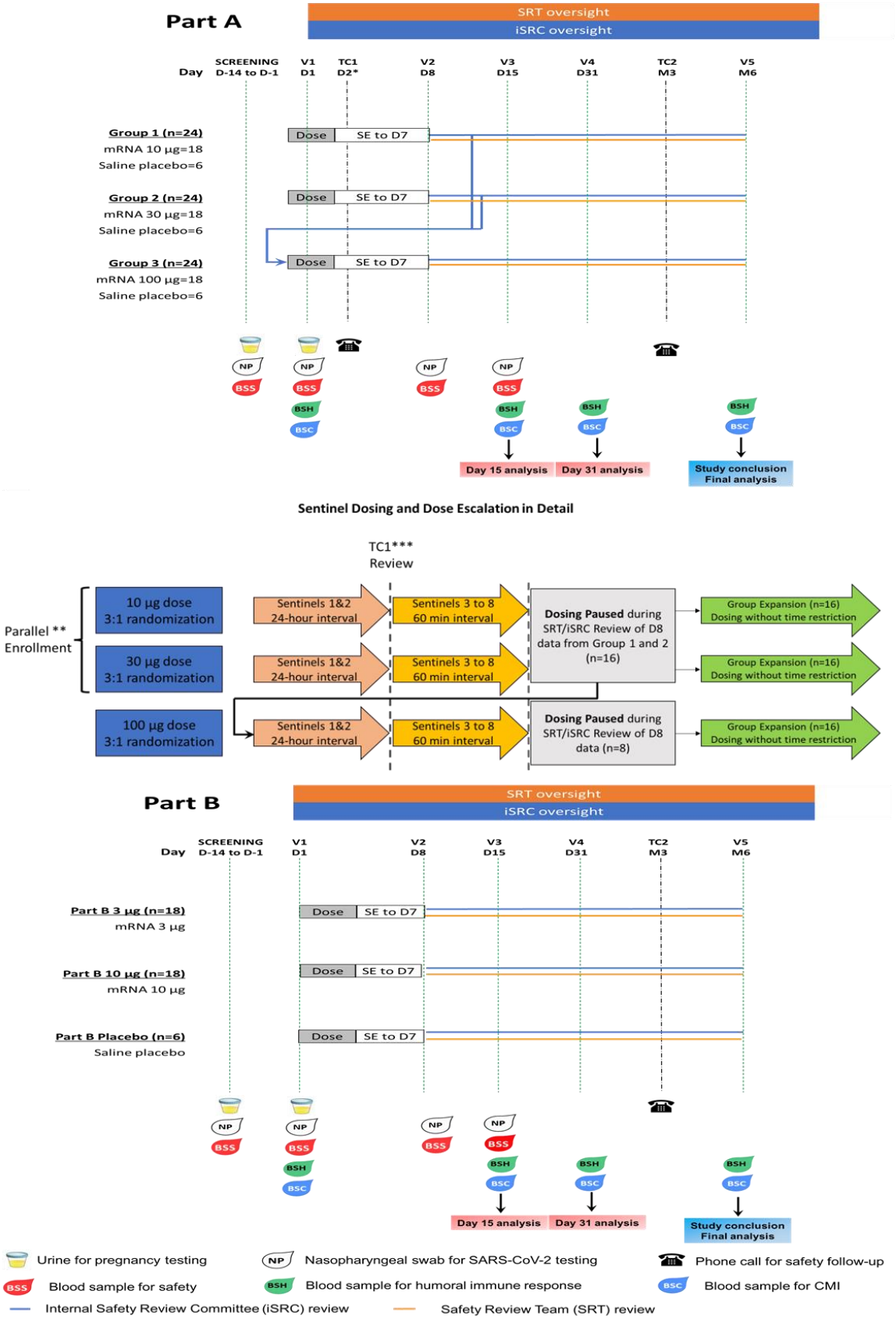
In Part B of the study, two doses (3 µg and 10 µg) of the mRNA-CR-04 vaccine will be evaluated. Approximately 42 eligible healthy adults, 18 to 49 years, inclusive, will be enrolled in Part B and will be randomly assigned in a 3:3:1 ratio:

- 18 participants will receive 3 µg of the investigational mRNA-CR-04 vaccine and
- 18 participants will receive 10 µg of the investigational mRNA-CR-04 vaccine and
- 6 participants will receive a saline placebo (sodium chloride [NaCl] isotonic solution [0.9%]).

Study duration for all the participants will be approximately 6 months, and they will be evaluated for safety, reactogenicity and immunogenicity. Safety monitoring and safety data review will be performed by a GSK SRT (blinded data review until Part A Day 15 interim analysis, unblinded data review subsequently) and a GSK iSRC (unblinded data review).

Overview of study design is presented in Section 4.1. Safety holding rules and safety monitoring are presented in Section 8.3.7.

Figure 1 Study design overview



CMI: Cell-mediated immunity; D: Day; M: Month; mRNA: mRNA-CR-04 vaccine; n: Number of participants; SE: Solicited events; TC: Telephone call; V: Visit.

* TC1 D2 only for sentinel participants in each group. ** The first participant is to be enrolled in Group 1. In addition to the defined intervals between doses within each group, an interval of at least 60 minutes will be maintained between the vaccination of sentinel participants across Group 1 and Group 2. *** TC1 review will be performed by the SRT on blinded data.

1.3. Schedule of Activities (SoA)

Table 1 SoA

Type of contact	Screening period	Visit 1	TC1*	Visit 2	Visit 3	Visit 4	TC2	Visit 5	Early termination	Unscheduled COVID-19+	Unscheduled cardiac evaluation	Notes
Time points		D1	D2	D8	D15	D31	M3	M6				
Window (D)	D–14 to –1	0	0	+2	±2	±3	±5	±7				
Assessment and sampling time points	Pre-Vacc	Pre-Vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc				
Screening												
Informed consent	●											Section 10.1.3
Inclusion/exclusion criteria	●	●										Section 5.1 and Section 5.2
Demography	●											Section 8.1.1
Medical history	●									●		Section 8.1.2
Vaccination history	●											Section 8.1.2
Physical examination	●	●***								●		Section 8.3.1
Vital signs measurement	●	●***								●		Section 8.3.1
Body temperature	●	●***								●		Section 8.3.2 The preferred location for measuring temperature will be: oral. Fever is defined as body temperature ≥38ºC/100.4ºF.
Pregnancy test **	●	●										Section 8.3.3
Study intervention												
Participant randomization		●										Section 6.3
Vaccine administration		●										Section 6.1
Initiation of eDiary		●										Section 8.1.3

Type of contact	Screening	Visit 1	TC1*	Visit 2	Visit 3	Visit 4	TC2	Visit 5	Early termination	Unscheduled COVID-19+	Unscheduled cardiac evaluation	Notes
Time points	**period**	**D1**	**D2**	**D8**	**D15**	**D31**	**M3**	**M6**				
Window (D)	**D–14 to –1**	**0**	**0**	**+2**	**±2**	**±3**	**±5**	**±7**				
Assessment and sampling time points	**Pre-Vacc**	**Pre-Vacc**	**Post-Vacc**	**Post-Vacc**	**Post-Vacc**	**Post-Vacc**	**Post-Vacc**	**Post-Vacc**				
Laboratory assessment												
SARS-CoV-2 N protein serology		●			●	●		●	●			Section 8.2.1
SARS-CoV-2 RT-PCR (nasopharyngeal swab)	●	●		●	●					●		Section 8.2.1
Blood sample for binding IgG		●			●	●		●	●			Section 8.2.1
Blood sample for neutralization		●			●	●		●	●			Section 8.2.1
Blood sample for PBMC ICS assay preparation		●			●	●		●	●			Section 8.2.1
Safety assessments												
Hematology and serum chemistry	●	●		●	●						●	Section 8.3.6
Cardiac troponin I	●			●							●	Section 8.2.1
Record any concomitant medication/vaccination	●	●		●	●	●	●	●	●	●		Section 6.8
Record solicited AEs in eDiary (up to 7 days after vaccination)		○		○								Section 8.4
Record unsolicited AEs (up to 30 days after vaccination)		●	●	●	●	●						Section 8.4
Reporting of SAEs, MAAEs, AESI (including COVID-19), and pregnancies		●	●	●	●	●	●	●	●	●	●	Section 8.4
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	Section 8.4
EKG	●			●							●	Section 8.3.4
Study Conclusion								●	●			

AE: Adverse event; AESI: Adverse events of special interest; D: Day; eCRF: electronic Case report form; eDiary: electronic Diary card; EKG: Electrocardiogram; GSK: GlaxoSmithKline Biologicals SA; ICS: Intracellular cytokine staining; IgG: Immunoglobulin G; M: Month; MAAE: Medically attended adverse event; N: Nucleocapsid; PBMC: Peripheral blood mononuclear cell; pIMD: potential Immune-mediated disease; RT-PCR: Real-time polymerase chain reaction; SAE: Serious adverse event; TC: Telephone call; Vacc: Vaccination.

Diagnosis of COVID-19 should be made in accordance with the World Health Organization [WHO, 2023] case definitions. Cases should be reported as AESIs or SAEs, and routine procedures for recording, evaluation, follow-up, and reporting of AESIs, and SAEs should be followed in accordance with the protocol-defined time periods.

* TC1 is only for sentinel participants in each group in Part A.

** Female participants of childbearing potential must perform a urine pregnancy test before the administration of the study intervention. For screening, if time allows, a serum pregnancy test can be done, in place of the urine pregnancy test, as per local requirements.

*** Physical examination, vital signs, and body temperature measurement at D1 will occur before vaccination.

+ Procedures apply to both suspected and convalescent visits for COVID-19.

Note: The double-line border following D15 indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to D15.

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

○ Is used to indicate a study procedure that requires documentation in the eDiary.

Table 2 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Screening → Visit 1 (D1)	1-14 days*	1-14 days
Visit 1 (D1) → TC1 (D2)	1 day	1 day
Visit 1 (D1) → Visit 2 (D8)	7 days	7-9 days
Visit 1 (D1) → Visit 3 (D15)	14 days	12-16 days
Visit 1 (D1) → Visit 4 (D31)	30 days	27-33 days
Visit 1 (D1) → TC2 (M3)	90 days	85-95 days
Visit 1 (D1) → Visit 5 (M6)	180 days	173-187 days

D: Day; M: Month; PCR: Polymerase chain reaction; TC: Telephone call.
* Visit 1 should take place no longer than 14 days after the Screening visit. All screening procedures, except the SARS-CoV-2 PCR test, need to be performed within 14 days of Visit 1 (see Section 8.1 and Section 8.3). A SARS-CoV-2 PCR test needs to be performed within 7 days of Visit 1. When applicable, a sample may be collected for repeat testing at any time (but only once to assess eligibility) before Visit 1. Only laboratory results from the repeat test, if it occurs, will be taken into consideration. The participant can only be assigned to a study intervention group once the investigator receives the results and confirms eligibility.

2. INTRODUCTION

2.1. Study rationale

As part of developing a novel mRNA vaccine platform, GSK selected the SARS-CoV-2 S glycoprotein as a model antigen (mRNA-CR vaccine). This is an exploratory, FTIH, observer-blind, randomized, controlled study, evaluating various doses of mRNA-CR-04 in individuals who have previously received:

- 2-dose primary series and booster dose(s) of an authorized or licensed mRNA COVID-19 vaccine (only Moderna or Pfizer vaccines) with the last booster dose administered at least 6 months or more prior to screening.

The safety, reactogenicity and immunogenicity of the mRNA-CR-04 vaccine administered in healthy adults previously vaccinated with a SARS-CoV-2 mRNA vaccine will be evaluated. The decision to move this mRNA construct and dose forward for the development of vaccines for a specific disease will be based on safety, reactogenicity, and immunogenicity profiles of the construct compared to the current standard of care.

2.2. Background

Due to the ongoing impact of COVID-19, there is a need for vaccines to provide protection against COVID-19 caused by SARS-CoV-2 variants of concern. As of 03 March 2023, more than 675 million cases have been reported worldwide, leading to more than 6.8 million deaths [Mathieu, 2023]. To date, there are multiple licensed or conditionally approved vaccines available that rely on a variety of vaccine technologies.

With the surge in Omicron predominance worldwide, its greater transmissibility, and a higher risk of SARS-CoV-2 reinfection with Omicron [Garcia-Beltran, 2021; Zhou, 2021], it is reasonable to anticipate an urgent need for booster vaccines to expand immunity against Omicron and additional future variants of concern. Bivalent boosters encoding Omicron BA.4/5 and the ancestral S protein sequences, followed by monovalent boosters encoding XBB.1.5 since 11 September 2023, have been authorized

for all doses administered to individuals 6 months of age and older [FDA, 2023a; FDA, 2023b].

Please refer to the current IB for information regarding preclinical studies of mRNA-CR-04 vaccine.

2.3. Benefit/risk assessment

Detailed information about the known and expected benefits and risks and expected AEs of mRNA-CR-04 vaccine can be found in the IB.

With any vaccine, administration site (e.g., pain, swelling, redness) and systemic (e.g., fever, fatigue, headache, myalgia) post-dosing events may occur within the first 3 days of study intervention administration, and are anticipated to be resolved within a few days of onset.

Syncope can occur following an injectable vaccine or even before any vaccination as a vasovagal response to the needle injection. Similarly, hypersensitivity reactions may also occur.

Currently, there are no identified preclinical risks for the investigational mRNA-CR-04 vaccine. However, the following important potential risks and mitigation strategies have been defined for this vaccine:

Risk Assessment

Important/potential/risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
All study vaccines		
Hypersensitivity reactions including allergic reactions such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine - administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Rüggeberg, 2007].	A history of hypersensitivity or severe allergic reaction (including anaphylaxis) is an exclusion criterion for study participation and a contraindication to vaccination. The onset of vaccine-related allergic symptoms is typically quite prompt. To treat participants with a serious allergic vaccination reaction, all participants will need to remain under observation (i.e., visibly followed; no specific procedure) at the study site for at least 60 minutes after vaccination. Participants will be instructed to contact the study site immediately for occurrence of any possible hypersensitivity reaction within 1 day following study intervention administration.
Bleeding following intramuscular injection	As with other intramuscular injections, study intervention should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant	To minimize the risk of bleeding, study intervention should be given with caution in individuals with thrombocytopenia or any coagulation disorder.

Important/potential/risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	therapy, to avoid the risk of hematoma following the injection.	Participants with any medical condition that in judgment of the investigator would make intramuscular injection unsafe will be excluded from study enrollment.
mRNA-CR-04 vaccine		
Myocarditis/pericarditis	Myocarditis/pericarditis are considered as an important identified risk for marketed mRNA COVID-19 vaccines [EMA, 2021a; EMA, 2021b; FDA, 2021a; FDA, 2021b] The estimated reporting rates of myocarditis in younger adults [25- to 29-year old] following the first and the second doses of BNT162b2 vaccine were 0.7 and 5.7 per 100 000, respectively and following the first and the second doses of mRNA-1273 vaccine were 1.8 and 11.2 per 100 000, respectively [CDC, 2021]. The same reporting trend was observed following booster mRNA vaccination, except for age, with most cases reported in older adults [ACIP, 2021].	Participants at increased risk of myocarditis/pericarditis or with medical history of myocarditis/pericarditis are excluded from study enrollment. Participants will also be instructed (via informed consent form) to be alert for symptoms of myocarditis/pericarditis and immediately contact the site if any of these symptoms occur. Participants will be tested for cardiac troponin I and undergo EKG at the screening and on D8 after study intervention administration. Participants will receive close medical supervision and medical assessments (e.g., laboratory testing) during the study. Moreover, myocarditis/pericarditis will be collected as an AESI and adjudicated (refer to Section 8.3.8,Section 8.4.4 and Section 10.3.5)
Vaccine-associated disease enhancement	Enhanced disease following vaccination has been observed in pre-clinical or clinical studies with various vaccines (e.g., RSV, Dengue, SARS) and the mechanism is poorly understood [Peeples, 2020]. While there are literature reports of enhanced disease in animals vaccinated with previous SARS vaccines, some other reports fail to see this effect.	During informed consent process, participants will be informed of this theoretical risk and asked to report any symptoms consistent with COVID-19 and/or for which they received medical attention at any point during the study. Any suspected, probable, or confirmed case of COVID-19 (regardless of severity) is an AESI; and will be captured and described (refer to Section 8.4.4 and Section 10.3.5)

AESI: Adverse event of special interest; EKG: Electrocardiogram; D: Day; RSV: Respiratory syncytial virus; SARS: Severe acute respiratory syndrome.

Benefit assessment

Participants may gain information about their general health status through medical evaluations/assessments associated with this study (i.e., physical examinations and blood testing [hematology and biochemistry data]).

Overall Benefit: Risk conclusion

The investigational mRNA-CR-04 vaccine is currently in an early stage of clinical development and vaccine efficacy, immunogenicity, and safety have not yet been demonstrated in humans.

Based on the available data for currently authorized/licensed mRNA COVID-19 vaccines, some potential risks have been defined. Appropriate safety monitoring and evaluation methodologies are in place to quickly identify any such events, should they occur.

Thus, while the benefit of this vaccine has not yet been proven, the anticipated potential risks for the mRNA-CR-04 vaccine are justified by the anticipated potential benefits.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Study objectives, endpoints and estimands

Objective(s)	Endpoints/Estimands
Primary	
• To evaluate the safety and reactogenicity of investigational mRNA-CR-04 vaccine up to D31	• Solicited administration site events and systemic events during the 7-day follow-up period after study vaccine administration (day of study vaccine administration and 6 subsequent days); • Unsolicited AEs during the 30-day follow-up period after study vaccine administration (day of study vaccine administration and 29 subsequent days); • Any hematological and biochemical laboratory abnormality during the 15-day follow-up period after study vaccine administration (day of study vaccine administration and 14 subsequent days); • MAAEs; SAEs; AESIs* up to D31.
Secondary Safety	
• To assess safety of investigational mRNA-CR-04 vaccine from study vaccine administration up to study conclusion.	• MAAEs; SAEs; AESIs* up to study conclusion (M6).
Secondary Immunogenicity	
• To evaluate the Ab functionality (neutralizing capacity induced by the mRNA-CR-04 vaccine against vaccine encoded SARS-CoV-2 and WT strains) up to study conclusion.	• Neutralizing titer GMTs against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint (D1, D15, D31, M6). • GMR from baseline (D1) of neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint. • Vaccine response rate based on neutralizing titers against vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint.
Tertiary	
• To describe serum-binding antibody (IgG) responses induced by the mRNA-CR-04 vaccine specific for vaccine encoded SARS-CoV-2 and WT strains S protein up to study conclusion.	• GMCs of binding IgG Ab specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains at each timepoint (D1, D15, D31, M6). • GMR from baseline of binding IgG Ab specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains S proteins at each timepoint. • Seroresponse rates based on binding IgG concentrations specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains S protein at each timepoint.

Objective(s)	Endpoints/Estimands
• To describe cell-mediated immune responses induced by the mRNA-CR-04 vaccine up to study conclusion.	• Frequency of CD4+/CD8+ T-cells specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains measured by intracellular cytokine staining assay at each time point (D1, D15, D31, M6). • Cellular immune responses including, but not limited to Th1 and Th2 profiles as determined by flow cytometry using ICS at each time point (D1, D15, D31, M6).
• To describe the incidence of confirmed symptomatic and asymptomatic SARS-CoV-2 infection.	• Percentage of laboratory-confirmed (N protein seroconversion) asymptomatic SARS-CoV-2 infection at each time point (D1, D15, D31, M6). • Percentage of laboratory-confirmed (RT-PCR) symptomatic SARS-CoV-2 infection at screening, D1, D8, D15, as well as at unscheduled visits.
• To evaluate the genetic sequence of SARS-CoV-2 variant S protein in confirmed (RT-PCR) SARS-CoV-2 positive participants.	• Comparison of SARS-CoV-2 S protein genetic sequence of viral isolates (when available) to the vaccine mRNA sequence • Identification of SARS-CoV-2 variants.
• To further characterize the humoral response (including, but not limited to functionality of antibodies) and cellular response, specific for the vaccine encoded SARS-CoV-2, WT and other relevant strains.	• S-specific responses at D1, D15, D31, M6 • Other read-outs may be performed if deemed necessary.

Ab: Antibody; AE: Adverse event; AESI: Adverse events of special interest; D: Day; GMR: Geometric mean ratio; GMT: Geometric mean titer; ICS: intracellular cytokine staining; IgG: Immunoglobulin G; M: Month; MAAE: Medically attended adverse events; N: Nucleocapsid; pIMD: potential Immune-mediated disease; RT-PCR: Real-time polymerase chain reaction; S: Spike; SAE: Serious adverse event; VAED: Vaccine associated enhanced disease; WT: Wild type.
*AESI include pIMDs, myocarditis/pericarditis, virologically confirmed COVID-19 cases and anaphylaxis or severe hypersensitivity within 24 hours after study vaccination (Section 8.4.4).

Details related to attributes of estimands covering intercurrent events and strategies, population, treatment condition, and population level summary will be provided in SAP.

4. STUDY DESIGN

4.1. Overall design

Experimental Design: Phase 1, observer-blind, randomized, placebo-controlled, multicenter, dose-escalation study to evaluate in Part A of the study, 3 doses (10 µg, 30 µg, and 100 µg) of the mRNA-CR-04 (Omicron BA.5 strain) vaccine (Figure 1) in 3 groups (Group 1, Group 2 and Group 3) (Table 4). Part B of the study will commence only after all Part A participants have completed their Day 15 study visits and the Day 15 interim analysis is completed. In Part B (Table 5), 2 doses (3 µg and 10 µg) of the mRNA-CR-04 (Omicron BA.5 strain) vaccine will be evaluated (Figure 1). The study will be conducted in the United States (US).

Duration of the study: Approximately 6 months after dosing.

Sentinel dosing: In Part A of the study, each group will have 8 sentinel participants (6 receiving the mRNA-CR-04 vaccine and 2 receiving a placebo) who will be enrolled and

vaccinated in each group. The first and second sentinel participant in each group will be vaccinated and followed-up for 24 hours before the next sentinel participant can be vaccinated. Vaccination of the remaining sentinel participants in the same group will then continue with an interval of at least 60 minutes between participants. Additionally, an interval of at least 60 minutes will be maintained between the vaccination of sentinel participants across groups.

Dose-escalation: In Part A of the study, enrollment of participants in Group 1 and Group 2 will be done in parallel with the first participant to be enrolled in Group 1. All safety data up to Day 8 post-vaccination from sentinel participants in both groups will be reviewed by the iSRC (unblinded review). The iSRC members will determine whether any of the pre-defined holding rules are met or if there is any other safety signal. If no safety signal is observed, vaccination of the non-sentinel participants in that group will continue. If no safety signal observed from sentinel participants in Group 1 and Group 2, enrollment and vaccination of the sentinel participants in Group 3 will be initiated. In Part B, irrespective of dose, all participants in the three study groups will be enrolled in parallel.

Safety Data: Safety data will be collected for 6 months post-vaccination. Solicited AEs will be collected for 7 days (day of vaccination and 6 subsequent days) and unsolicited AEs will be collected up to Day 31. MAAEs, SAEs, pIMDs, and AESIs will be collected for the duration of the study. In addition to the review of unblinded data by iSRC, blinded data until Part A Day 15 interim analysis, and unblinded data subsequently, will be regularly reviewed by the SRT. For more detailed information, refer to Section 8.3 and Section 8.4.

For the vendors that will perform key study-related duties or activities, please refer to the separate list of vendors.

Table 4 and Table 5 describe the Part A and Part B study groups, interventions, and blinding, respectively.

Table 4 Part A study groups, interventions, and blinding

Study groups	Number of participants	Age (Min-Max years of age)	Study intervention(s)/vaccine(s) mode of administration		Blinding
					Screening→Visit 5
Group 1	18	18 – 49	mRNA-CR-04 vaccine 10 µg	Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm.	Observer-blind
	6	18 – 49	Saline placebo (NaCl [0.9%])		
Group 2	18	18 – 49	mRNA-CR-04 vaccine 30 µg	Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm.	Observer-blind
	6	18 – 49	Saline placebo (NaCl [0.9%])		
Group 3	18	18 – 49	mRNA-CR-04 vaccine 100 µg	Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm.	Observer-blind
	6	18 – 49	Saline placebo (NaCl [0.9%])		

NaCl: Sodium chloride.

Table 5 Part B study groups, interventions, and blinding

Study groups	Number of participants	Age (Min-Max years of age)	Study intervention(s)/vaccine(s) mode of administration		Blinding
Part B 3 µg	18	18 – 49	mRNA-CR-04 vaccine 3 µg	Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm.	Observer-blind (except sponsor)
Part B 10 µg	18	18 – 49	mRNA-CR-04 vaccine 10 µg	Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm.	Observer-blind (except sponsor)
Part B Placebo	6	18 – 49	Saline placebo (NaCl [0.9%])	Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm.	Observer-blind (except sponsor)

NaCl: Sodium chloride.

4.2. Scientific rationale for study design

To ensure maximum safety of the participants, as this will be the first time that the mRNA-CR-04 vaccine will be administered in humans, the study will follow an observer-blind design with staggered enrollment and dosing for Part A of the study, with study holding rules and close safety monitoring throughout the study as specified in Section 4.1 and Section 8.3.7. Part B of the study adds an even lower dose (3 µg) of

mRNA-CR-04 vaccine group to allow exploration of a wider range of vaccine doses, as well as a repeat of the Part A low dose (10 µg) of mRNA-CR-04 vaccine group, which may assist in standardizing the new 3 µg dose group in Part B to the earlier Part A study groups.

4.3. Justification for dose

The proposed doses will be 3 µg, 10 µg, 30 µg, and 100 µg. The monovalent SARS-CoV-2 mRNA vaccines (Pfizer-BioNTech Comirnaty mRNA vaccine [FDA, 2023a] and Spikevax Moderna COVID-19 Vaccine [FDA, 2023b]) have been licensed in the US as a 2 or 3-dose primary series. Bivalent formulations of the Moderna and Pfizer-BioNTech COVID-19 vaccines encoding S protein sequences from Omicron BA.4/5 and the ancestral strain followed by monovalent boosters encoding XBB.1.5 since 11 September 2023, have been authorized for primary and booster vaccinations [FDA, 2023a; FDA, 2023b].

The maximum planned dose is 100 µg. The rationale for evaluating doses from 3 µg to 100 µg is based on the following considerations:

- The optimal dose required to confer cross-protective immunity against non-Omicron variants, including new/emerging variants needs to be determined.
- Moderna has evaluated doses up to 250 µg (2-dose regimen) in their Phase 1 studies [Jackson, 2020].
- The doses of the authorized bivalent booster vaccines from Pfizer-BioNTech and Moderna are 30 µg and 50 µg, respectively. The initial starting dose of 10 µg of the mRNA-CR-04 vaccine in Part A of the study is well below these doses.

4.4. End-of-study definition

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

EoS: LSLV (Visit 5, Month 6) or date of the last testing released of the human biological samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

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 jeopardize 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 prior to dose administration:

1. Written or witnessed informed consent obtained from the participant prior to performance of any study-specific procedure.
2. Participants, who in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the eDiary and study procedures).
3. Has received 2 doses of primary series and booster dose(s) of an authorized or licensed mRNA COVID-19 vaccine (only Moderna or Pfizer vaccines) with the last booster dose administered at least 6 months or more prior to screening and has provided documentation of receiving the vaccination series (e.g., vaccination card).
4. Negative for SARS-CoV-2 infection by RT-PCR test at screening within 7 days prior to study vaccination.
5. Is a male or nonpregnant female of 18 to 49 years, inclusive, at screening.
6. If the participant is a WOCBP, the participant agrees to practice true abstinence or use at least 1 highly effective form of contraception for at least 30 days prior to study vaccination up to 1 month after study vaccination.
7. Agrees to refrain from blood or plasma donation from screening and up to 6 months after vaccination.
8. Is healthy or medically stable as determined by investigator judgment based on medical history, clinical laboratory tests, vital sign measurements, and physical examination findings.

5.2. Exclusion criteria

The following criteria should be checked at the time of screening and on D1 prior to dose administration. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

1. Has a new onset, clinically significant, abnormal biochemistry or hematology finding (defined as ≥Grade 1) at screening (participants with Grade 1 laboratory abnormalities that have been stable for at least 6 months before enrollment may be included in the study).
2. Has any medical disease or condition that, in the opinion of the investigator, precludes study participation. This includes any acute, subacute, intermittent, or chronic medical disease or condition that would place the participant at an unacceptable risk of injury, render the participant unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the participant's successful completion of the trial.
3. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

4. History of myocarditis, pericarditis, second and third degree heart block or idiopathic cardiomyopathy, or presence of any medical condition that increases risk of myocarditis or pericarditis, including cocaine abuse, cardiomyopathy, endomyocardial fibrosis, hypereosinophilic syndrome, hypersensitivity myocarditis eosinophilic granulomatosis with polyangiitis, persistent myocardial viral infection (e.g., due to enterovirus or adenovirus).
5. Has an acute febrile illness with a temperature ≥38.0°C or ≥100.4°F observed by the participant or at the study site within 72 hours prior to study vaccination. Participants with suspected COVID-19 symptoms (Section 8.4.4.2.2) should be excluded and referred for medical care.
6. Has a history of hypersensitivity or severe allergic reaction, including anaphylaxis, generalized urticaria, angioedema, and other significant reactions to any previous vaccine, or any component of the study vaccine.
7. Has a body mass index >40 kg/m².
8. Has had known close contact with anyone who had a confirmed SARS-CoV-2 infection within 14 days before study vaccination.
9. Has a history of documented SARS-CoV-2 infection or COVID-19 within 6 months before the date of screening visit.
10. Has any self-reported or medically documented clinically significant medical or psychiatric condition. Significant medical conditions include, but are not limited to, the following:
    a. Moderate or severe respiratory disease (e.g., chronic obstructive pulmonary disease, asthma).
    b. Uncontrolled hypertension, defined as an average systolic blood pressure ≥140 mmHg or an average diastolic blood pressure ≥90 mmHg, based on an average of up to 3 blood pressure measurements.
    c. Clinically significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease).
    d. Neurological or neurodevelopmental conditions (e.g., Down syndrome, dementia, chronic migraine not controlled by medication, epilepsy, stroke or seizures in the last 3 years, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis, or transverse myelitis).
    e. Ongoing malignancy or recent diagnosis of malignancy in the last 5 years (excluding basal cell and squamous cell carcinoma of the skin).
    f. Tuberculosis or non-tuberculosis mycobacterial infection.
    g. Autoimmune disease, including hypothyroidism without a defined nonautoimmune cause.
    h. Immunodeficiency of any cause, including from solid organ transplant, blood, or bone marrow transplant, or use of other immune-weakening medicine.
    i. Type 1 or 2 diabetes mellitus regardless of disease control.
11. Has any of the following self-reported or medically documented risk factors for severe COVID-19:

a. Chronic kidney disease
b. Cerebrovascular disease
c. Cystic fibrosis
d. Chronic liver disease
e. Pulmonary fibrosis

5.2.2. Prior/concomitant therapy

12. Has participated or plans to participate in another investigational study involving any investigational drug or device within 60 days or 5 half-lives, whichever is longer, before study vaccination and throughout the study.
13. Has received a licensed or authorized non-mRNA COVID-19 vaccine (primary series or booster dose).
14. Has received or plans to receive any licensed vaccine within 4 weeks before or after study vaccination. Inactivated vaccines for influenza are permitted during the study if they are administered at least 14 days before or after study vaccination.
15. Is planning to receive an authorized or licensed COVID-19 booster vaccination for the duration of the study (for participants who are not covered by local recommendations to receive booster per current standard of care) OR is planning to receive an authorized or licensed COVID-19 booster vaccination on or before Day 31 of the study (for participants covered by local recommendations to receive booster).
16. Has received or plans to receive immunoglobulins or any blood or blood products within 90 days before study vaccination and throughout the study.
17. Reports chronic use (more than 14 continuous days) of any medication that may be associated with changes in immune function including, but not limited to, systemic corticosteroids exceeding 20 mg/day of prednisone equivalent, allergy injections, immunoglobulins, interferons, immunomodulators, cytotoxic drugs, or other similar or toxic drugs within 6 months of study vaccination. Note: The use of low-dose topical, ophthalmic, inhaled, intra-articular and intranasal steroid preparations is permitted.

5.2.3. Other exclusions

18. Pregnant or lactating female.
19. Female participant planning to become pregnant or planning to discontinue contraceptive precautions within 1 month following study vaccination.
20. Participant is an employee or family member of the investigator or study site personnel.

5.3. Screen failures

A screen failure is an individual who consents to participate in this study but is not entered in the study/assigned to a study intervention.

Limited data for screening failures (including informed consent, inclusion/exclusion criteria, demographic data, pregnancy reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

If the investigator believes there is a reasonable justification to do so, all screening procedures may be repeated (maximum 1 re-screening per participant is allowed) under a new participant number. The participant can only be randomized into the study once the investigator receives the results and confirms the eligibility criteria.

Participants with hematological/biochemical values out of normal range which are expected to be temporary may be re-screened at a later date, as per the above conditions.

5.4. Criteria for temporarily delaying enrollment, randomization and study intervention administration

Enrollment, randomization and study intervention administration may be postponed within the 14-day screening interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of enrollment and/or study intervention administration. Refer to the Section 1.3 for definition of fever and oral temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- If antipyretics and/or analgesics and/or antibiotics have been used within 3 days prior to study intervention administration.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1. Study interventions administered

Refer to Section 1.2 for the study intervention administration schedule. Table 6 and Table 7 describe study interventions to be administered for Part A and Part B, respectively.

Table 6 Part A study interventions administered

	mRNA-CR-04		Placebo
Study intervention[#]: Group 1	COV08A/DL001Z		PL001Z
Group 2	COV08B/DL001Z		PL001Z
Group 3	COV08C		PL001Z
Study intervention formulation[#]: Group 1	GSKVx000000037755 (Dose Aa GSKVx000000037754); Excipients; Water for injections	Excipients; Water for injections	Excipients; Water for injections
Group 2	GSKVx000000037755 (Dose Ab GSKVx000000037754); Excipients; Water for injections	Excipients; Water for injections	Excipients; Water for injections
Group 3	GSKVx000000037755 (Dose Ac GSKVx000000037754); Excipients; Water for injections		Excipients; Water for injections
Presentation: Group 1	Concentrate for dispersion for injection (vial)	Solution for dispersion for injection (vial)	Solution for injection (vial)
Group 2	Concentrate for dispersion for injection (vial)	Solution for dispersion for injection (vial)	Solution for injection (vial)
Group 3	Dispersion for injection (vial)		Solution for injection (vial)
Type:	Investigational		Placebo
Product category:	Biologic		Drug
Route of administration:	IM		IM
Location	Deltoid		Deltoid
Directionality	NA		NA
Laterality*	Non-Dominant		Non-Dominant
Number of doses to be administered	1		1
Volume to be administered by dose **	0.3 mL		0.3 mL
Packaging and labeling:	Refer to the PM for more details		Refer to the PM for more details
Manufacturer:	GSK		Hospira

Ab: Antibody; IM: Intramuscular; GSK: GlaxoSmithKline Biologicals SA; NA: Not applicable; PM: Pharmacy manual.
*The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.
**Refer to the PM for the volume after reconstitution.
[#]Coding serves for internal sponsor anonymization

Table 7 Part B study interventions administered

	mRNA-CR-04				Placebo
Study Groups	**Part B 3 µg**		**Part B 10 µg**		**Part B Placebo**
Study intervention#	COV08D/DL001Z		COV08A/DL001Z		PL001Z
Study intervention formulation#:	GSKVx000000037755 (Dose Ad GSKVx000000037754); Excipients; Water for injections	Excipients; Water for injections	GSKVx000000037755 (Dose Aa GSKVx000000037754); Excipients; Water for injections	Excipients; Water for injections	Excipients; Water for injections
Presentation:	Concentrate for dispersion for injection (vial)	Solution for dispersion for injection (vial)	Concentrate for dispersion for injection (vial)	Solution for dispersion for injection (vial)	Solution for injection (vial)
Type:	Investigational		Investigational		Placebo
Product category:	Biologic				Drug
Route of administration:	IM				IM
Location	Deltoid				Deltoid
Directionality	NA				NA
Laterality*	Non-Dominant				Non-Dominant
Number of doses to be administered	1				1
**Volume to be administered by dose ** **	0.3 mL				0.3 mL
Packaging and labeling:	Refer to the PM for more details				Refer to the PM for more details
Manufacturer:	GSK				Hospira

Ab: Antibody; IM: Intramuscular; GSK: GlaxoSmithKline Biologicals SA; NA: Not applicable; PM: Pharmacy manual.
*The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.
**Refer to the PM for the volume after reconstitution.
#Coding serves for internal sponsor anonymization

6.2. Preparation, handling, storage, and accountability

The study interventions 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.

Only unblinded staff should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the PM for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization and blinding

This is a dose-escalation, observer-blind, randomized study.

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the individuals who have consented to participate in the study by using an automated internet-based system (e.g., IRT).

6.3.2. Randomization to study intervention

The randomization of study interventions will be performed using the IRT system.

6.3.3. Intervention allocation to the participant

In Part A of the study, approximately 72 participants will be enrolled with 24 participants per group. These 24 eligible participants will be randomly assigned to investigational mRNA-CR-04 vaccine or saline placebo in a (3:1) ratio. In Part B of the study, approximately 42 participants will be enrolled and randomly assigned to 3 µg investigational mRNA-CR-04 vaccine, 10 µg investigational mRNA-CR-04 vaccine, or saline placebo in a (3:3:1) ratio.

6.3.4. Blinding and unblinding

In Part A of the study, data will be collected in an observer-blind manner. 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. To do so, study interventions will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review, or the entry of any study endpoint data (i.e., reactogenicity, safety, immunogenicity). In Part B of the study (i.e., following the Part A Day 15 interim analysis), continuation of the observer-blind design will be restricted to study participants and site personnel involved in the clinical evaluation of the participants, while sponsor personnel will no longer remain blinded to treatment assignment.

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

In case of emergency, the investigator can have unrestricted, immediate and direct access to the participant's study intervention information via the IRT. The investigator may contact Signant Health support (refer to Table 8) if help is needed to access participant's study intervention information (i.e., if the investigator is unable to access IRT).

A physician other than the investigator (e.g., an emergency room physician) or participant may also request emergency access to the participant's study intervention information via the investigator.

Table 8 Contact information for emergency unblinding

Signant Health support Available 24/24 hours and 7/7 days
The Signant Health support is available by phone and email US: 1-888-794-0122 IRTHelpdesk@SignantHealth.com

A participant may continue in the study if that participant's treatment assignment is unblinded.

GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the 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 the dose of study vaccine directly from the investigator or designee, under medical supervision. The date and time 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

Not applicable.

6.7. Treatment of overdose

An overdose is any dose of study vaccine given to a participant that exceeds the planned dose for an individual participant within a given group.

There is no specific treatment recommended for an overdose.

Any overdose must be promptly reported to the CRO team within 24 hours. Overdose itself is not to be reported as an AE. However, any AEs associated with the overdose are to be reported in the relevant AE/SAE sections of the eCRF.

In the event of an overdose, the investigator should:

1. Contact the CRO medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 3 days. Refer the participant to a higher level of care as clinically indicated.
3. Document the quantity of the excess dose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant therapy

At each study visit/contact, the investigator(s) or their delegate(s) should question the participant 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 medications, except vitamins and dietary supplements, administered during the entire study.
- Any concomitant use of antipyretic/analgesic medication from Day 1 to Day 7 after vaccination.
- Any concomitant vaccination administered in the period starting 30 days before study intervention administration and ending 30 days after vaccination.
- Any booster COVID-19 vaccines received during the study will be recorded.
- All concomitant medication associated with an AE, including vaccines/products, administered after study intervention vaccination (Day 1 to Day 31).
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to Section 5.2.2 and Section 9.3.1 for further details.

- All concomitant medication which may explain/cause/be used to treat an SAE/AESI including vaccines/products, as defined in Section 8.4.1. These must also be recorded in the electronic AE report.

The medical monitor 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

Not applicable.

7.1.1. Contraindications to subsequent study interventions administration

Not applicable.

7.2. Participant discontinuation/withdrawal from the study

Individual participants may withdraw from the study at any time at their own request for any reason without prejudice to their future medical care by the investigator or at the study site.

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 them 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 planned in the protocol.

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

At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

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

Reasons	Additional items/Sub-reasons
AE	Unsolicited AE Solicited AE
Lost to follow-up	Participant Relocated Other, specify Unknown
Study Terminated by Sponsor	
Withdrawal by Participant (not due to an AE)	Participant Relocated Other, specify
Other	Specify

AE: Adverse event

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.5).

7.3. Lost to follow-up

Participants will be considered 'lost to follow-up' if they fail to return for scheduled visits and cannot be contacted by the study site.

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Immediate safety concerns should be discussed with the CRO team 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 summarized in the SoA (Section 1.3).

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

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

Procedures conducted as part of routine clinical management (e.g., hematologic profiles), and obtained before the participant signed the ICF, may be used for screening and/or for

establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA in Section 1.3).

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

During special circumstances (e.g., COVID-19 pandemic), certain study procedures may be adapted to protect the participant's welfare, and as far as possible to ensure the potential benefit to the participant and promote data integrity. See Section 8.10.

8.1. Administrative procedures

All screening procedures, except the SARS-CoV-2 PCR test, need to be performed within 14 days of Visit 1 (see Section 5.1). A SARS-CoV-2 PCR test needs to be performed within 7 days of Visit 1. A sample may be collected for repeat testing at any time (but only once to assess eligibility) before Visit 1.

8.1.1. Collection of demographic data

At screening, record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF.

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

8.1.2. Medical/vaccination history

At screening, obtain the participant's medical/vaccination history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, vaccination history, signs and/or symptoms present prior to study intervention in the eCRF.

8.1.3. Distribution of eDiary or installing the application for devices

Participants will be encouraged to bring their own devices at screening visit, or if not feasible, at Visit 1 (Day 1). The study staff will check the compatibility of participant's device (e.g., smart phone or tablet) with respect to eDiary application.

At Visit 1 (Day 1), participant will download the eDiary application on his/her own electronic device or will receive an electronic device to record information related to his/her health and participation in the study. The participant will also be trained on the use of eDiary.

Refer to Section 8.4.1 for details of collection of safety information and Section 10.3.5 for guidelines.

For the vendors that will perform eDiary-related activities, please refer to the separate list of vendors.

8.2. Immunogenicity assessments

Blood samples will be taken to assess both the humoral and cellular immune responses induced by the vaccine candidate on Day 1, Day 15, Day 31, and Month 6.

In addition, 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 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.

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.

8.2.1. Biological samples

Table 9 Biological samples

Sample type	Quantity	Unit	Timepoint	Subset name
Nasopharyngeal swab for SARS-CoV-2 test	NA	NA	Screening (D-7 to D-1)	All screened participants
			Visit 1 (D1)	All enrolled participants
			Visit 2 (D8)	
			Visit 3 (D15)	
Blood for FSH	~2.5	mL	Screening (D-14 to D-1)	Female participants to confirm non-childbearing potential
Blood for Troponin I	~2.5	mL	Screening (D-14 to D-1)	All screened participants
			Visit 2 (D8)	All enrolled participants
Blood for hematology/ biochemistry	~6	mL	Screening (D-14 to D-1)	All screened participants
			Visit 1 (D1)	All enrolled participants
			Visit 2 (D8)	
			Visit 3 (D15)	
Blood (serum) for vaccine-induced humoral immune response and to assess SARS-CoV2 N protein serology	~15	mL	Visit 1 (D1)	All enrolled participants
			Visit 3 (D15)	
			Visit 4 (D31)	
			Visit 5 (M6)	
Blood (PBMCs) for cellular immune response	~50	mL	Visit 1 (D1)	All enrolled participants
			Visit 3 (D15)	
			Visit 4 (D31)	
			Visit 5 (M6)	

D: Day; FSH: Follicle stimulating hormone; M: Month; N: Nucleocapsid; NA: Not applicable; PBMC: Peripheral blood mononuclear cell.

8.2.2. Laboratory assays

Following laboratory assays will be performed (Table 10).

- PCR assay will be used to detect SARS-CoV-2 infection. If the sample is positive and sufficient material is available, sequencing of the SARS-CoV-2 isolate will be performed by genomic RNASeq.
- Serological assay to monitor the asymptomatic infection will be performed using an ECL to measure serum-binding Abs IgG levels specific for N protein of SARS-CoV-2.
- The vaccine-induced humoral immunity will be evaluated using serological assays determining the capacity of the serum of SARS-CoV-2 vaccinated participants to neutralize pseudoviruses bearing S protein from vaccine encoded SARS-COV-2 and from the WT (D614G).
- Further characterization of the humoral immune response will be performed using ECL for measurement of IgG antibodies binding to the SARS-CoV-2 S protein (at least vaccine encoded SARS-CoV-2 variant and WT).
- The cell-mediated immunity will be evaluated by assessing the frequency of SARS-CoV-2 S-specific CD4+ and CD8+ T-cells expressing specific activation or immune markers using ICS per million of total CD4+ or CD8+ T-cells respectively.

Table 10 Laboratory assays

Assay Type	System	Component	Challenge	Method	Laboratory**
Humoral immunity (antibody determination)*	Serum	Anti-S binding IgG Ab	NA	ECL	PPD
	Serum	Anti-SARS-CoV-2 neutralizing titer		Pseudo Neutralization assay	Nexelis
Cell-mediated immunity	PBMCs	CD4+/CD8+ T-cells expressing IL-2/IFNγ/TNFα/IL-13/IL-17/4-1BB/CD40L	Peptide pools covering the SARS-CoV-2 S protein	ICS	GSK
Detection of SARS-CoV-2 Infection	Serum	Anti-N IgG Ab	NA	ECL	PPD
Detection of SARS-CoV-2 Infection	Nasopharyngeal Swab	SARS-CoV-2 RNA	NA	RT-PCR	PPD
Sequencing of SARS-CoV-2 Isolates	Nasopharyngeal Swab	SARS-CoV-2 RNA	NA	RNASeq	PPD

Ab: Antibody; CD40L: Cluster of differentiation 40 ligand; 4-1BB: CD137 (tumor necrosis factor receptor superfamily 9); CRO: Contract research organization; ECL: Electro-chemiluminescence assay; GSK: GlaxoSmithKline Biologicals SA; ICS: Intracellular cytokine staining; IgG: Immunoglobulin G; IFNγ: Interferon gamma; IL-2: Interleukin-2; IL-13: Interleukin-13; IL-17: Interleukin-17; NA: Not applicable; N: Nucleocapsid; PPD: Pharmaceutical Product Development; RNASeq: RNA Sequencing; RT-PCR: Real-time polymerase chain reaction; S: Spike; TNFα: Tumor necrosis factor alpha; WT: Wild type.
* Measurement of humoral immunity against vaccine encoded SARS-CoV-2 and WT strains.
** Refer to the list of clinical laboratories for details.

Please refer to Section 10.2 for further details.

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

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

8.2.3. Immunological read-outs

Table 11 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (D1)	Pre-Dose 1	All enrolled participants	72 (Part A) + 42 (Part B)	SARS-CoV-2 neutralizing titer
				Anti-S binding IgG Ab
				Anti-N IgG Ab
				S-specific CD4+/CD8+ T-cells
Visit 3 (D15)	14 days Post-Dose 1	All enrolled participants	72 (Part A) + 42 (Part B)	SARS-CoV-2 neutralizing titer
				Anti-S binding IgG Ab
				Anti-N IgG Ab
				S-specific CD4+/CD8+ T-cells
Visit 4 (D31)	30 days Post-Dose 1	All enrolled participants	72 (Part A) + 42 (Part B)	SARS-CoV-2 neutralizing titer
				Anti-S binding IgG Ab
				Anti-N IgG Ab
				S-specific CD4+/CD8+ T-cells
Visit 5 (M6)	6 months Post-Dose 1	All enrolled participants	72 (Part A) + 42 (Part B)	Anti-SARS-CoV-2 neutralizing titer
				Anti-S IgG Ab
				Anti-N IgG Ab
				S-specific CD4+/CD8+ T-cells

Ab: Antibody; D: Day; IgG: Immunoglobulin G; M: Month; N: Nucleocapsid; S: Spike.

8.2.4. Cytology

Not applicable.

8.2.5. Immunological correlates of protection

No validated mechanistic immunological correlate of protection has been demonstrated so far for the antigens used in the study intervention.

8.3. Safety assessments

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

8.3.1. Physical examination

- At screening and prior to dosing at Visit 1 (Day 1), the investigator will perform a physical examination of the participant. The following information needs to be recorded in the eCRF: weight, oral temperature, resting vital signs (before blood collection for laboratory test); systolic/diastolic blood pressure and heart rate after at least 10 minutes of rest. If the participant reported any pre-existing medical condition, the investigator would extend the physical examination according to his/her medical judgment to ensure that the participant meets all the eligibility criteria. Height and BMI will only be recorded at screening.

- A targeted physical examination at each study visit after the Screening visit, will be performed only if the participant 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 study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.4 for the list of criteria for temporary delay of study intervention administration.
- Treatment of any abnormality observed during post-vaccination visits must be performed according to local medical practice outside this study or by referral to an appropriate health care provider and recorded as AE.

8.3.2. Pre-dosing body temperature

The body temperature of each participant needs to be measured orally prior to the study vaccine administration and recorded in the eCRF. If the participant has fever on the day of dosing, the study intervention administration visit will be rescheduled. Refer to the SoA (Section 1.3) for the definition of fever for this study and preferred location for body temperature measurement.

8.3.3. Pregnancy test

Female participants of childbearing potential must perform a urine pregnancy test before the administration of the study intervention. At screening, if time allows, a serum pregnancy test can be done, in place of the urine pregnancy test, as per local requirements. 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 Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

For WONCBP, document the specific reason for not performing a pregnancy test in the eCRF.

8.3.4. EKGs

- 12-lead EKGs will be obtained as outlined in the SoA (see Section 1.3) using an EKG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.3.5. Warnings and precautions to administration of study intervention

Vital signs, including oral temperature, systolic/diastolic blood pressure and heart rate after at least 10 minutes of rest for each participant needs to be measured prior to administration of study intervention, i.e., at Visit 1. Collected information will be recorded in the eCRF.

8.3.6. Clinical safety laboratory tests

- See Section 10.2.1 for the list of clinical laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 31 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - 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 Section 10.3.1 and Section 10.3.2).
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
- Analyses of safety laboratory samples collected at Day 1 through the EoS will be performed at the central laboratory using the same grading standards.
- Laboratory data will be graded according to the FDA guidance for industry "Toxicity grading scale for healthy adults and adolescent volunteers enrolled in preventive vaccine clinical trials" dated September 2007 [FDA, 2007]. These laboratory values serve as guidelines and are dependent upon laboratory normal parameters. Normal reference ranges should be provided to demonstrate that they are appropriate. Any laboratory parameters not listed in Table 19 and Table 20 (Section 10.2.2) will not be graded and will be assessed on case-by-case basis.

8.3.7. Study holding rules and safety monitoring

Safety monitoring is specified in the SoA (Section 1.3), Section 8.3.7.1 and Table 12.

For the vendors that will perform safety monitoring activities, please refer to the separate list of vendors.

8.3.7.1. Staggered administration of study intervention

Part A of the study will be conducted in a staggered manner to ensure maximum safety of the participating participants.

- Within each group, 8 sentinel participants (6 receiving the mRNA-CR-04 vaccine and 2 receiving the placebo) will first be enrolled and vaccinated.
- Enrollment of participants in Group 1 and Group 2 will be done in parallel with the first participant to be enrolled in Group 1. The first and second sentinel participant in each group will be vaccinated and followed-up for 24 hours before the next sentinel participant can be vaccinated. If no safety concerns are identified (as confirmed through individual phone call – TC1, see Table 1), vaccination of the remaining sentinel participants in the same group will then continue with an interval of at least 60 minutes between participants. Additionally, an interval of at least 60 minutes will be maintained between the vaccination of sentinel participants across groups.
- If no safety concerns are identified by the iSRC during the review of unblinded Day 8 safety data of sentinel participants from Group 1 and Group 2, the remaining participants in these groups may receive the study intervention without limitation of the number of participants per day or the time between consecutive participants. Additionally, vaccination of sentinel participants in Group 3 may be initiated.
- If no safety concerns are identified by the iSRC review of unblinded Day 8 safety data of sentinel participants from Group 3, the remaining participants in Group 3 may receive the study intervention without limitation of the number of participants per day or the time between consecutive participants.

All participants will be closely observed (visibly followed, no specific procedure) during the 60 minutes after dose administration.

In addition to iSRC, blinded data will be reviewed by the SRT. The SRT and iSRC will meet regularly to review safety data throughout the study and may request escalation to the GSB to address any potential safety concerns or study holds at any point during the study. See Section 8.3.7.3.

In Part B of the study, irrespective of dose, all participants will be enrolled in parallel, and the SRT will also be able to review unblinded data.

8.3.7.2. Outcome of safety evaluation

Outcome of safety evaluations will be documented and provided in a written way to the investigator. Refer to iSRC charter for more details.

- If **no safety** signal is observed, the favorable outcome of the safety evaluations by the iSRC will be documented and provided, authorizing the investigator to start the enrollment and study intervention administration to the remaining participants in the group and the sentinel participants in the next group.
- If **a safety signal** is observed during the safety evaluations or if any of the holding rules is met, the iSRC Chair is responsible for the urgent communication and escalation of the concern to the GSB. The GSB will decide and communicate whether to suspend, modify or continue the conduct of the study on all groups or on selected groups, including the rationale for the decision to put the study intervention administration on hold or not.
- The study sponsor will be accountable for notifying the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups to the CRO. The CRO will be responsible to inform all investigators of this decision.

8.3.7.3. Study holding rules

The safety holding rules are defined in the Table 12. Holding rules 1a-d will be assessed by the investigator on a continuous basis. Meeting any of these holding rules will trigger a hold of study intervention administration irrespective of number of participants enrolled and/or timing of the event. Holding rules 2a-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 (expressed as percentage of participants to be evaluated) i.e., 3 out of 6 sentinel participants or 30% of all participants, whichever is met earlier.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, missed visits due to study intervention related AEs, Grade 1 and Grade 2 solicited and unsolicited AEs in the 7-day follow-up period (Day 1 to Day 7) and unsolicited AEs collected from Day 8 to Day 31 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.

Table 12 Study holding rules

Holding rule	Event (per dose and per individual study group)	Number of participants to pause vaccination in all groups, pending further evaluation by iSRC
1a	Death or any life-threatening SAE regardless of causality	≥1
1b	Any non-life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per investigator or sponsor assessment	≥1
1c	Any withdrawal from the study (by investigator or participant request) following a Grade 3 AE	≥1
1d	Any administration site or systemic solicited AE leading to hospitalization, 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 events, with an event onset within the 7-day (Day 1-7) post-vaccination period	≥3/6 or 30%**
2b*	Any Grade 3 solicited systemic events, with an event onset within the 7-day (Day 1-7) post-vaccination period	≥3/6 or 30%**
2c*	Any Grade 3 unsolicited AE, that can be reasonably attributed to the vaccination as per investigator or sponsor assessment, with an event onset within the 7-day (Day 1-7) post-vaccination period OR Any Grade 3 or above abnormality in pre-specified hematological or biochemical laboratory parameters with an event onset within the 8-day (Day 1-8) post-vaccination period except for non-clinically significant leukopenia	≥2/6 or 10%***

AE: Adverse event; iSRC: Internal safety review committee; SAE: Serious adverse event.
*Refer to the FDA guidance for industry "Toxicity grading scale for healthy adults and adolescent volunteers enrolled in preventive vaccine clinical trials" [FDA, 2007]. Any laboratory parameters not listed in Section 10.2.2 will not be graded and will be assessed on case-by-case basis.
**3/6 sentinel participants or 30% of all participants, whichever is met earlier.
***2/6 sentinel participants or 10% of all participants, whichever is met earlier.

Rule 2a-2c will be analyzed and reviewed during the scheduled iSRC meetings. During these scheduled iSRC meetings, iSRC will decide to:

- allow for dosing of the remaining non-sentinel participants (12 receiving mRNA-CR-04 and 4 receiving placebo) within the same group
- allow for randomization of the sentinel participants in the next group.

More details on the composition, objectives, and responsibilities of the iSRC, and the schedule and conduct of the iSRC meetings will be described in the iSRC charter.

If a holding rule is met, the investigator must suspend enrollment and administration of the study intervention and inform the CRO team immediately (holding rules 1a-d). Refer to Table 16 for contact information.

The CRO team will inform the investigator if holding rules 2a-c are met. Investigators will be responsible to inform the IRB/IEC if a holding rule has been met.

The following communication sequence must be followed when a holding rule 1a-1d is met:

- The concerned site staff must put study intervention randomization and administration on hold.
- The concerned site staff must immediately inform the CRO team contact defined in the Section 8.4.6.
- Enrollment and intervention allocation through IRT will be stopped on a study level.
- The CRO team will inform all investigators about the stopping of enrollment and intervention.
- All informed site staff will confirm to the CRO team that action has been taken providing appropriate documentation to the CRO team.
- The CRO team will inform GSK and provide the blinded data to GSK's CSL for further SRT and GSK GSB review.
- The CRO team will forward the relevant unblinded safety information to iSRC for evaluation.
- Based on the recommendation from iSRC, GSK's GSB will make the decision whether the study can resume, be modified, or stopped. GSK will notify the CRO team on this decision. The CRO team will notify all investigators on this decision.
- Depending on the outcome of the safety evaluation, the study will be re-started, terminated, or resumed under a protocol amendment.

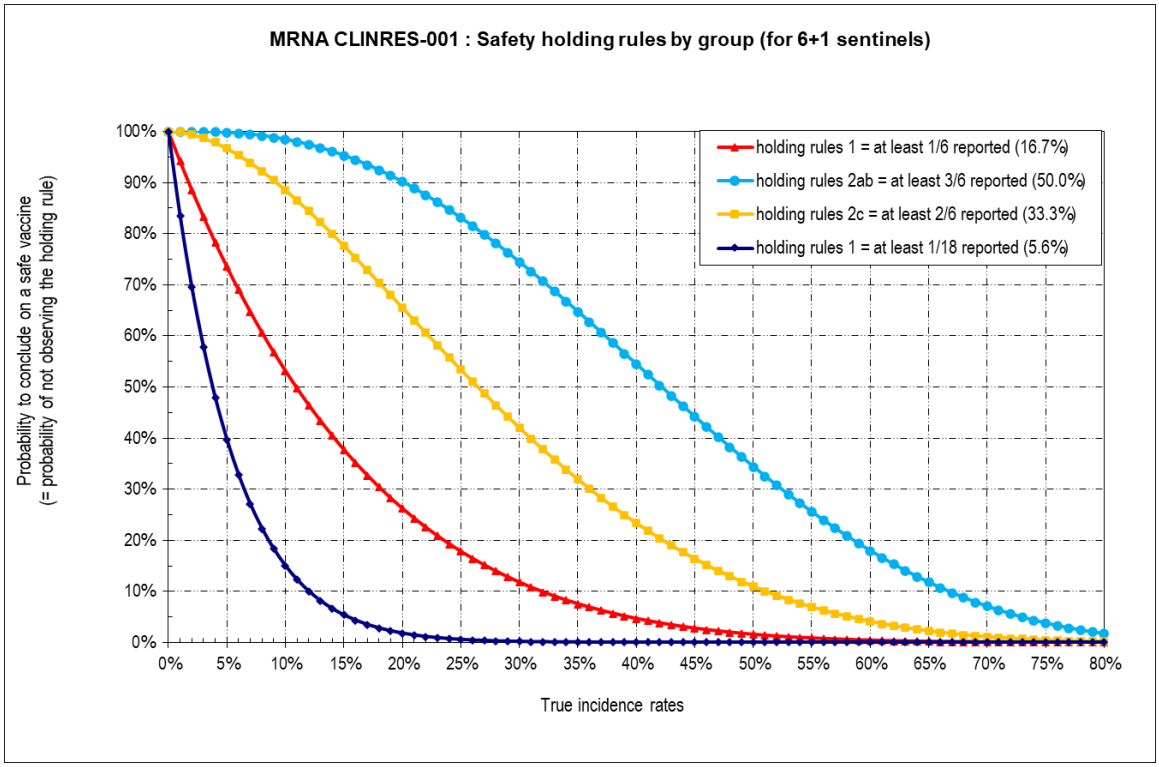
The following communication sequence must be followed when a holding rule 2a-2c is being met:

- The study CSL will ensure that the CRO team is notified upon meeting holding rules 2a-2c.
- The CRO team will inform all the sites that a holding rule is met. Following this notification, the study intervention administration should be put on hold.
- All informed site staff will confirm to the CRO team that action has been taken providing appropriate documentation to the CRO team.
- GSK will further evaluate the case with the iSRC and GSK GSB and will take the decision to stop or to restart the study intervention administration or to amend the protocol. GSK will notify the CRO team on this decision and the CRO team will inform all site staff.

Risk assessment:

- Figure 2 illustrates that with 6 participants receiving the mRNA-CR-04 vaccine per group:
  - Rule 1: when at least 1 SAE is observed within 6 participants receiving the mRNA-CR-04 vaccine, there is 90% probability of not holding for a 1.7% SAE true incidence and 80% (=1-20%) probability of holding it for an SAE true incidence >23%.
  - Rule 2a-2b: when at least 3 participants with an AE are observed within 6 participants receiving the mRNA-CR-04 vaccine, there is 90% probability of not holding for a 20% AE true incidence and 80% (=1-20%) probability of holding it with a true AE incidence >58%.
  - Rule 2c: when at least 2 participants with an AE are observed within 6 participants receiving the mRNA-CR-04 vaccine, there is 90% probability of not holding for a 9% AE true incidence and 80% (=1-20%) probability of holding it with a true AE incidence >42%.
  - With 18 participants receiving the mRNA-CR-04 vaccine, and rule 1 (1/18), there is 90% probability of not holding for a 0.59% AE true incidence and 80% (=1-20%) probability of holding it with a true incidence >8.5%.

Figure 2 Probability of not meeting holding rules 1 and 2 for 8 participants per study group



8.3.7.4. SRT and iSRC evaluation

The study will be overseen by an iSRC operating under a charter. Core members of the iSRC will include a GSK safety physician, a CSL and a biostatistician who are not otherwise involved in the conduct of the project. The iSRC safety reviews will be conducted using unblinded data. The iSRC will have access to the participant randomization and will review unblinded data.

In addition to the iSRC, the project SRT will review blinded data until the Part A Day 15 interim analysis, and unblinded data subsequently, on a regular basis throughout the study.

The iSRC will review accumulated unblinded safety data of the sentinel participants of each group up to 7 days post-vaccination. The iSRC will include all safety data sources in their Day 8 safety review (i.e., solicited safety data, unsolicited safety data, SAEs and AESIs, as well as laboratory safety data). If no pre-defined holding rule is met (refer to Section 8.3.7.3) or if no safety signal is observed the remaining participants in the group can be vaccinated and vaccination in the next group can be initiated.

In case the iSRC, through the in-stream data monitoring of all the accumulated safety data available detects that a holding rule is met, the study vaccination will be temporarily paused in all study groups and sites pending review of safety data by the iSRC. The iSRC will make relevant recommendations to the GSB chair(s), who will make the final decision whether vaccination can be safely resumed or not.

In addition, at any time during the study, if one of the holding rules 1a through 1d (refer to Table 12 for details) is met, the investigator will immediately inform the CRO team. Vaccination will be paused and an urgent ad-hoc meeting of the iSRC will be called to thoroughly review the event(s) and recommend to the GSB whether vaccination can be safely resumed or not. The GSB chair(s) will make the final decision whether vaccination can be safely resumed or not.

In Part B of the study, the iSRC will only be requested to review unblinded data if a study holding rule is met or if the SRT identifies a safety concern through in-stream data monitoring of unblinded data.

8.3.8. Cardiac adjudication

Myocarditis and pericarditis are considered as important potential risk and are collected as AESI. All surveillance EKGs occurring at Screening, Day 8, and unscheduled visits, will be reviewed by an independent external cardiologist in a blinded fashion to identify potential myocarditis or pericarditis cases. All EKGs identified with changes suggestive of potential myocarditis and pericarditis and related available medical records requested from treating cardiologists evaluating potential cases of myocarditis and pericarditis, will then be provided to an independent external adjudication committee for case adjudication according to the case definition from the Brighton Collaboration [Sexson, 2022]. The committee members will remain blinded to study intervention assignment.

For details on who will perform the reading and adjudication activities, please refer to the separate list of vendors.

8.4. AEs, SAEs, and other safety reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up AEs that are serious, considered related to study intervention or study procedures, AESIs for this study and AEs leading to discontinuation (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver or surrogate).

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

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

All SAEs will be collected from the start of study intervention until Visit 5 at the time points specified in the SoA (Section 1.3).

SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

All AEs will be collected from the start of study intervention until Visit 4 at the timepoints specified in the SoA (Section 1.3).

Table 13 Timeframes for collecting and reporting of safety information

Event	Screening	Dose 1					Study Conclusion
		D1	D8	D15	D31	M3	M6
Administration site and systemic solicited events*		D 1-7					
Unsolicited AEs		D1-31					
AEs/SAEs leading to withdrawal from the study							
MAAEs							
SAEs							
SAEs related to the study intervention							
SAEs related to study participation** or concurrent GSK medication/vaccine							
pIMDS							
AESIs							
Pregnancy							

Event	Screening	Dose 1					Study Conclusion
		D1	D8	D15	D31	M3	M6
Pregnancy outcomes							
Concomitant medications							

AE: Adverse events; AESI: Adverse event of special interest; D: Day, GSK: GlaxoSmithKline Biologicals SA; MAAEs: Medically attended adverse event; M: Month; pIMDs: potential Immune-mediated diseases; SAEs: Serious adverse events.

* Administration site and systemic solicited events will be collected through eDiaries.

** Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

The shaded region in the table indicates time period of data collection.

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

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 13.

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

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning/eDiaries of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

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

8.4.4. AESI

8.4.4.1. pIMDs

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 etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 14.

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

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

Table 14 List of pIMDs

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include “Interstitial lung disease”, “Pulmonary fibrosis”, “Immune-mediated pneumonitis”) • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
Endocrine disorders	
Addison’s disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow’s disease	• Includes Marine Lenhart syndrome and Graves’ ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III

Medical Concept	Additional Notes
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic lupus Erythematosus	• Includes Lupus associated conditions (e.g., cutaneous lupus erythematosus, lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)

Medical Concept	Additional Notes
Systemic Scleroderma (systemic sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory demyelinating variants	Includes the following: • Acute necrotizing myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g., optic neuritis) • Idiopathic nerve palsies/paresis (e.g., Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome

Medical Concept	Additional Notes
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
Goodpasture syndrome	• Frequently used related terms include "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"

Medical Concept	Additional Notes
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)
Immunoglobulin G4 related disease	
Langerhans cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

IgA: Immunoglobulin A; IgM: Immunoglobulin M.

8.4.4.2. Other AESIs

- Myocarditis and pericarditis
- Virologically confirmed COVID-19 cases
- Anaphylaxis or severe hypersensitivity within 24 hours after study vaccination

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

8.4.4.2.1. Myocarditis and pericarditis: definitions and assessment

All potential cases of myocarditis and pericarditis will be provided to the independent external adjudication committee for case adjudication according to the case definition from the Brighton Collaboration [Sexson, 2022].

Source documentation of suspected cases of myocarditis and pericarditis to be provided for adjudication as it becomes available may include (but are not limited to) the following:

- Clinical notes (including history, physical examination, EKG findings)
- Emergency department notes (including history, physical examination, EKG findings)
- Hospital discharge summary
- Clinical laboratory values
- Concomitant medications

- Chest X-ray reports
- Cardiac imaging

Following adjudication, all probable and definitive cases of myocarditis and pericarditis will be reviewed by SRT (blinded data review until Part A Day 15 interim analysis, unblinded data review subsequently) and iSRC (unblinded data review). An ad-hoc iSRC will be conducted on receiving any probable or definitive cases of myocarditis and pericarditis. An independent external cardiologist may be part of iSRC to provide input on the potential myocarditis and pericarditis cases.

Clinical myocarditis/pericarditis:

The participants reporting acute chest pain, shortness of breath or other signs/symptoms of myocarditis/pericarditis within 6 weeks after vaccination must be evaluated by a cardiologist with evaluation and management following current practice guidelines (e.g., American heart association or local standard of care).

The changes suggestive of myocarditis and pericarditis (but not limited to) are listed below:

- EKG changes:
  - ST segment or T wave abnormalities (elevation or inversion)
  - Paroxysmal or sustained atrial or ventricular arrhythmias
  - AV nodal conduction delays or intraventricular conduction defects.
  - An abnormal troponin I value (> 2 ULN of baseline value) that is confirmed abnormal on repeat testing.
- Cardiac imaging:
  - Echocardiogram: New left or right ventricular function abnormalities including: segmental wall motion abnormalities; decreased ejection fraction (EF <55% for ≤54 yrs; or <50% for >55 yrs); global systolic or diastolic function depression/abnormality; ventricular dilation or wall thickness change; pericardial effusion or intracavitary thrombi
  - Cardiac MRI: Patchy edema on T2 weighted images or late gadolinium enhancement on T1 weighted images with increased enhancement ratio between myocardial skeletal muscle involving ≥1 non-ischemic regional distribution with recovery

  The participants will be followed-up until the resolution of symptoms and/or cardiac troponin levels return back to normal.

***Asymptomatic myocarditis/pericarditis*:**

At the Day 8 (Visit 2), all participants will be assessed by 12-lead EKG for evidence of asymptomatic myocarditis or pericarditis, based on evidence that rare cases of myocarditis or pericarditis have occurred most frequently within 7 days of vaccination

[CDC, 2023]. All participants will also have a 12-lead EKG examination at screening, to provide a baseline for comparison.

Asymptomatic acute myocarditis/pericarditis is defined as electrocardiographic changes suggestive of acute myocardial injury occurring in an asymptomatic participant within 6 weeks after administration of a COVID-19 mRNA vaccine, if other causes of acute cardiac disease are excluded. If any of the EKG changes suggestive of myocarditis and pericarditis listed above are detected at the surveillance EKG occurring at the Day 8 visit, the findings will be reviewed by the investigator.

If deemed appropriate the participant will be referred to a local cardiologist. If a diagnosis of myocarditis or pericarditis is confirmed, then the participant will be further evaluated and receive cardiology consultation, including cardiac enzyme assessment, echocardiography, or other assessments deemed clinically warranted by the treating clinician.

8.4.4.2.2. SARS-CoV-2 infection and COVID-19 definitions and assessment

Vaccine efficacy will not be evaluated in this study, but all laboratory-confirmed asymptomatic SARS-CoV-2 infections should be reported by the participant and documented as AEs, while virologically confirmed cases of COVID-19 are reported as AESIs. Any available isolate genotyping results will also be requested. Participants will be instructed to inform the investigator in the event of a positive SARS-CoV-2 diagnostic test. Serology testing for SARS-CoV-2 N protein will be performed pre-vaccination and post-vaccination to monitor for undetected SARS-CoV-2 infections at the time points specified in the SoA (Section 1.3).

All participants with suspected COVID-19 are required to have an unscheduled visit for suspected COVID-19, as detailed in the SoA (Section 1.3). At this visit, participants will undergo the following assessments:

- Medical history
- SARS-CoV-2 RT-PCR (nasopharyngeal or mid-turbinate swab)
- Physical examination
- Vital sign measurements
- Body temperature
- Review of AEs
- Concomitant medication/vaccination

All participants with confirmed COVID-19 are required to have an unscheduled COVID-19 convalescent visit as detailed in the SoA (Section 1.3). At this visit, participants will undergo the following assessments:

- Medical history
- SARS-CoV-2 RT-PCR (nasopharyngeal or mid-turbinate swab)

- Physical examination
- Vital sign measurements
- Body temperature
- COVID-19 evaluation
- Review of AEs
- Concomitant medication/vaccination

To complete the COVID-19 evaluation, the investigator will review the history of the participants, including medical records to define the severity of COVID-19.

Any confirmed cases of SARS-CoV-2 infection or COVID-19 during the study will be assigned one of the following definitions and recorded in the eCRF:

Asymptomatic SARS-CoV-2 infection:	Laboratory-confirmed SARS-CoV-2 by RT-PCR or SARS-CoV-2 N protein seroconversion without any of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea
COVID-19:	Virologically confirmed SARS-CoV-2 by RT-PCR with 1 or more of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea
Severe COVID-19:	Virologically confirmed SARS-CoV-2 infection with any 1 of the following: • Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/ FiO2 < 300 mm Hg) • Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO) • Evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors) • Significant acute renal, hepatic, or neurologic dysfunction • Admission to a hospital or an intensive care unit • Death

8.4.5. Regulatory reporting requirements for SAEs/AESIs

- Prompt notification by the investigator to the sponsor of an SAE/AESI is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/AESI/pregnancy, it must be reported to the CRO medical monitor using the required documentation and within the timeframes mentioned in Table 15. This is essential for GSK to meet legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.
- 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 Section 10.3.5.7 for further details regarding the reporting of SAEs/AESIs/pregnancies.

Table 15 Timeframes for submitting SAE, AESI, pregnancy and other events reports to CRO

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ⌗	electronic AE report	24 hours*	electronic AE report
Pregnancies	24 hours*	electronic pregnancy report	24 hours *	electronic pregnancy report
AESIs	24 hours** ⌗	electronic AE report	24 hours*	electronic AE report

AE: Adverse event; Adverse event of special interest; SAE: Serious adverse event.
* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.
⌗ For each SAE/AESI, the investigator(s) must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.

8.4.6. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until Day 31.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor. See Table 15 for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.3.5.7. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

Table 16 Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

Study contact for questions regarding SAEs, AESIs, pregnancies	**Study contact for reporting of study holding rules**
If a SAEs, AESIs, pregnancies are reported, the investigator must inform the CRO medical monitor	If a holding rule is met, the investigator must immediately inform the CRO medical monitor.
Back up study contact for reporting SAEs, AESIs, pregnancies Available 24/24 hours and 7/7 days:	**Back up study contact for escalation of holding rules** Available 24/24 hours and 7/7 days:
CRO hotline **North America:** +1 800 201 8725 (phone) +1 888 488 9697 (fax)	

8.4.8. Participant card

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

8.5. Pharmacokinetics

Not applicable.

8.6. Genetics

Not applicable.

8.7. Biomarkers

Not applicable.

8.8. Immunogenicity assessments

Immunogenicity is described in Section 8.2.

8.9. Health outcomes

Not applicable.

8.10. Study procedures during special circumstances

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

- Further in-person clinic visits may be suspended.
- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.
- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the safety period for collection of solicited events following Visit 2 (Day 8), inclusive of the allowable window period).

- Visits for suspected COVID-19 may take place in a different location* other than the study site or at participant's home. If this is not feasible, then the medical evaluation of COVID-19 may take place virtually with documentation of event by telephone/telemedicine.
- 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.

  *It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to the EMA guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.

Impact on the PPS for immunogenicity will be determined on a case-by-case basis.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

There is no hypothesis testing in this study; all analysis will be performed in a descriptive manner. Means and proportions for different objectives will be computed with their 95% CIs.

9.2. Sample size determination

The sample size is based on clinical considerations to inform dose regimen decisions for continued clinical development.

With 18 participants receiving mRNA-CR-04 vaccine in each group, there is a 60.3% probability to observe at least 1 AE if the incidence rate is 5% and 85% probability to observe at least 1 AE if the incidence rate is 10%.

With 16 participants receiving mRNA-CR-04 vaccine in each group (PPS for immunogenicity, 10% unevaluable), and a standard deviation of 0.45 for $\log_{10}$ transformed increase from Day 1, the ratio of the upper limit of a 2-sided 95% CI and the point estimate of GMR is 1.74.

9.3. Analysis sets

Table 17 Analysis sets

Analysis set	Description
Screened	All participants who were screened for eligibility.
Enrolled	Participants who completed the informed consent process, meet screening/eligibility criteria and undergone an invasive procedure. Note: screening failures (who never passed screening even if re-screened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.
Exposed	All participants who received the dose of the study intervention. Analysis per group using the enrolled set based on the administered intervention.
Per Protocol	All eligible participants who received dose of study intervention as per protocol, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination, and who have values for pre-dose and post-dose neutralizing antibody titer against pseudovirus bearing S protein data for the relevant timepoint, and without major protocol deviations. The PPS for immunogenicity will be defined by time point.
Solicited Safety	All participants who received the dose of the study intervention (Exposed Set) who have reported the presence or absence of any solicited AE at least once.

AE: Adverse event; D: Day; S: Spike; PPS: Per Protocol Set

9.3.1. Criteria for elimination from analysis

If a participant meets one of the criteria mentioned below, they may be eliminated from per protocol analysis.

- Receive any of the medications/products/vaccines listed in Section 5.2.2.
- Incur an intercurrent medical condition that could alter their immune response (i.e., varicella, HIV, lymphoma) or are confirmed to have an alteration of their initial immune status.
- Major protocol deviation(s) linked to the eligibility criteria (Section 5.1 and Section 5.2).
- Study intervention not administered as specified by the protocol.
- Failure to comply with the post-dose immunogenicity blood sampling schedule at a given timepoint (Section 1.3).
- Other major protocol deviation during vaccination phase that led to exclusion.

The SAP will provide a complete list of criteria for elimination from PP analyses.

9.4. Statistical analyses

The SAP will be finalized prior to FSFV and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

For the vendors that will perform statistical activities, please refer to the separate list of vendors for details.

9.4.1. Primary endpoint

Analysis of primary safety endpoints will be performed on the Exposed Set, except for solicited AEs, which will be performed on the Solicited Safety Set. The analysis will be performed separately for study Part A and Part B participants. In addition, pooled analyses where groups common in Part A and Part B are combined as one group respectively will be performed.

Statistical analysis methods

The number and percentage of participants reporting AEs up to 30 days after the dose (Day 31):

- At least one administration site event (solicited and unsolicited), with at least one systemic event (solicited and unsolicited) and with any AE (solicited and unsolicited) during the 7-day and 30-day follow-up period will be tabulated by treatment. Same tabulations will be performed for Grade 3 AEs (all and causally related) and for any causally related AEs.
- Each individual solicited administration site event (any grade and Grade 3) and solicited systemic event (any grade and Grade 3) during the 7-day follow-up period will be tabulated by maximum intensity per participant for each treatment group.
- Fever will be reported as number and percentage of participants reporting temperature per 0.5°C cumulative increments as from ≥38°C or 100.4°F during the 7-day follow-up period (i.e., on the day of study intervention administration and 6 subsequent days) and will be tabulated for each treatment group.
- At least one unsolicited AE during the 30-day follow-up period after the dose, as classified by the MedDRA SOC and PT will be tabulated by treatment group. The same tabulation will be performed for Grade 3, any causally related, Grade 3 causally related unsolicited AEs and unsolicited AEs with medically attended visits.
- For each treatment group and for each hematology and biochemistry parameter:
  - The number and percentage of participants having hematology and biochemistry results below or above the laboratory normal ranges will be tabulated by time point.
  - The maximum grading post-dose up to Day 15 will be tabulated versus baseline (Day 1, or if not available, closest visit available to D1 before IMP administration). Grades will be based on the FDA guidance for industry "Toxicity grading scale for healthy adults and adolescent volunteers enrolled in preventive vaccine clinical trials" (Section 10.2.2).
- At least one MAAE, SAE and AESIs after the dose, as classified by the MedDRA SOC and PT, will be tabulated by treatment group. The same tabulation will be performed for causally related MAAEs, SAEs and AESIs during this period. The detailed listings of SAEs, AESIs and COVID-19 cases will also be produced.

- At least one concomitant medication (any medication or any antipyretic) during the 7-day follow-up period and during the 30-day follow-up will be summarized by treatment group.

9.4.2. Secondary endpoints/estimands analyses

9.4.2.1. Safety endpoints

Analysis of secondary safety endpoints will be performed on the Exposed Set. The analysis will be performed separately for study Part A and Part B participants. In addition, pooled analyses where groups common in Part A and Part B are combined as one group respectively will be performed.

Statistical analysis methods

The number and percentage of participants with **AEs up to study conclusion (Month 6)**:

- At least one MAAE, SAE and AESIs after the dose, as classified by the MedDRA SOC and PT, will be tabulated by treatment group. The same tabulation will be performed for causally related MAAEs, SAEs and AESIs during this period. The detailed listings of SAEs, AESIs and COVID-19 cases will also be produced.
- A listing of AEs/SAEs leading to withdrawal from the study will be provided.

9.4.2.2. Immunogenicity endpoints

The analysis of the secondary immunogenicity endpoints will be performed on the PPS separately for study Part A and Part B participants. In addition, pooled analyses where groups common in Part A and Part B are combined as one group respectively will be performed. If more than 10% of participants are eliminated from any of the PPS in any treatment group, a sensitivity analysis will be carried out using the Exposed Set.

Statistical analysis methods

Following **humoral immune responses** (neutralizing titer) will be summarized by treatment group using descriptive statistics, using corresponding blood sample collected for assessment of humoral immune responses:

- Neutralizing titer (GMT) against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains will be tabulated with 95% CI and represented graphically.
- GMR from baseline of neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection time point after administration of study intervention over time point before administration of study intervention will be tabulated with 95% CI.
- GMTs and GMRs from baseline of neutralizing titer, with their 95% CI, using an ANCOVA on log-transformed titer with treatment group as a fixed factor, and Day 1

baseline value as a covariable. GMTs and GMRs will also be represented graphically. Once Part B data are available, Part A and Part B data will be pooled together for model based analyses. When pooled, the study part will be added as a fixed factor and adjusted GMT/GMR will be estimated under Part A condition. Groups common in Part A and Part B will be combined as one group respectively for the pooled analysis.

- Percentage of participants with vaccine responses of a 4-fold increase from Day 1, with their exact 95% CI will be tabulated.

9.4.3. Analyses of exploratory immunogenicity endpoints

Additional exploratory immunological assays evaluating S-specific or disease-related antigen specific humoral or cellular immune responses, including but not limited to antibody functionality (Fcγ R binding capacity, IgG affinity), isotype titer and isotype avidity, deep immunophenotyping of cellular responses might also be performed. The analyses will be performed separately for study Part A and Part B participants. In addition, pooled analyses where groups common in Part A and Part B are combined as one group respectively will be performed. Appropriate pooled analyses, such as the ANCOVA planned on neutralizing antibody titers will also be performed on the IgG antibody responses.

Analysis of tertiary endpoints detailed in Section 3 will be described in the SAP.

9.5. Interim analyses

No interim analysis requiring statistical adjustment will be performed. However, analyses to evaluate objectives and endpoints will be performed in steps. The sequence of analyses is described below.

9.5.1. Sequence of analyses

- In preparation of the safety review during the dose-escalation safety lead-in, analyses of available safety data will be performed
- **Day 15 interim analysis** for each group in Part A of the study will include all the data (Day 1 and Day 15) pertaining to primary and secondary safety; humoral immunogenicity (including at least neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-COV-2 endpoints). This analysis will be performed when all data of each study group up to Day 15 (i.e., data that are as clean as possible) are available.
    - Results of this analysis will be presented in a Day 15 statistical analysis report.
    - This analysis will be performed by independent unblinded statistician who will be unblinded for this analysis, who will generate a statistical report by treatment group but no individual listings.
        - The investigators and study participants will stay blinded (i.e., will not have access to the individual participant treatment assignment) until EoS.

- A similar to Part A Day 15 interim analysis for participants in Part B of the study may be conducted separately or incorporated into a Day 31 interim analysis.
- **Day 31 interim analysis** for each group in Part A of the study will include all the data (Day 1, Day 15, and Day 31) pertaining to primary and secondary safety; humoral immunogenicity (including at least neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-COV-2 endpoints). This analysis will be performed when all data of each study group up to Day 31 (i.e., data that are as clean as possible) are available.
  - Results of this analysis will be presented in a Day 31 statistical analysis report.
  - The investigators and study participants will stay blinded (i.e., will not have access to the individual participant treatment assignment) until EoS.
- A similar to Part A Day 31 interim analysis for participants in Part B of the study may be conducted separately or incorporated into the final analysis.
- **The final analysis** will include all the data pertaining to primary and secondary safety and immunogenicity endpoints, and any available tertiary endpoint(s). This analysis will be performed at the EoS when all data up to study conclusion (Month 6) are available. This includes Day 1, Day 15, Day 31, and Month 6, as all the data analyzed in the Day 15 and Day 31 analyses will be included in the final analysis as well.

The final study report will contain at least the final analyses of all primary and secondary endpoints, including individual listings.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These analyses will be documented in annex(es) to the study report.

9.5.2. Statistical consideration for Interim analyses

Not applicable.

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 CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines

- Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., eDiary) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

The investigator(s) or their representative(s) must fully explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Freely given and written informed consent must be obtained from each participant, as appropriate, prior to participation in the study.

The content of the ICF must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized 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.

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

A physical or digital copy of the ICF must be provided to the participants.

Participants who are re-screened are required to sign a new ICF.

10.1.4. Data protection

Participants will be assigned a unique identifier by the investigator. 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.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.

The participants must be informed that:

- Their personal study-related data will be used by the sponsor in accordance with local data protection law.
- Their medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The participants 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

The study will be overseen by an SRT, and iSRC operating under a charter.

The SRT is an internal team, with representatives of different functions (including safety physician, a CSL and a biostatistician) involved in the conduct of the study/project.

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

The iSRC is an internal committee including a GSK safety physician, a CSL and a biostatistician who are not otherwise involved in the conduct of the project.

More details on the composition, objectives, and responsibilities of the iSRC will be described in the charter.

Furthermore, to enhance independent, systematic, and standardized identification, processing and review of probable or confirmed cases of myocarditis or pericarditis; an independent external cardiologist will review and assess all performed EKGs (Screening, Day 8, unscheduled visits) and an independent adjudication committee will perform case adjudication according to the case definition from the Brighton Collaboration [Sexson, 2022]. Details of data collection and frequency of data review are provided in Section 8.4.4.2.1.

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 study registers.

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

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

GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

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 Definition of terms for the exact definition of essential and source documents). The document storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the

requirements for certified copies (see Definition 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 study records that include all pertinent observations on each of the site's study participants (see Definition 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 Definition 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 authorized 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.

QTLs will be pre-defined in the centralized monitoring 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 summarized in the CSR.

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

When copies of source documents are shared externally for review by a central reader mechanism (e.g., independent external cardiologist, adjudication committee), documents are stored by the external body for approximately 3 years.

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 Definition of terms.

Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g., independent external cardiologist, adjudication committee). The non-exhaustive list of documents shared to inform the central reader may include EKG reports, lab data, medical records etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.9. Study and site start and closure

First act of recruitment

The start of study is defined as FSFV at a country-level.

Study/Site termination

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

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

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

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

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

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

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

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 ICMJE.

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Protocol required safety laboratory assessments

The tests detailed in Table 18 will be performed by the CRO PPD.

Table 18 Protocol required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Prothrombin Time / INR	RBC Indices: MCV MCH %Reticulocytes		WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	BUN		AST	Total and direct bilirubin
	Creatinine		ALT	
			ALP	
Other tests	• Follicle stimulating hormone (as needed in WONCBP only) • Cardiac troponin (troponin I) • [Serum or urine hCG pregnancy test (as needed for WOCBP)] The results of each test carried out locally must be entered in the eCRF.			

NOTES:
All events of ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.
All events of Troponin I ≥ 2 x baseline value, may require clinical review.
Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; eCRF: electronic Case report form; hCG: human Chorionic gonadotropin; INR: International normalized ratio; IEC: Independent ethics committee; IRB: Institutional review board; MCH: Mean corpuscular hemoglobin; MCV: Mean corpuscular volume; RBC: Red blood cell; SAE: Serious adverse event; ULN: upper limit of normal; WBC: White blood cell; WONCBP: Woman of non-child-bearing potential; WOCBP: Woman of childbearing potential.

10.2.2. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials

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 19 Toxicity grading scales for biochemistry parameters evaluated in the current study*

Serum **	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)***
BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
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
ALP – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Bilirubin – when accompanied by any increase in liver function test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; ULN: upper limit of normal.

* Toxicity grading taken from FDA guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials [FDA, 2007].

** 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 characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Table 20 Toxicity grading scales for hematology parameters evaluated in the current study*

Hematology**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (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 – 1 500	1,501 – 5,000	> 5,000	Hypereosinophilic
Platelets decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
Prothrombin Time – increase by factor	1.03 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	>1.25 x ULN

ULN: Upper limit of the normal range; WBC: White blood cell.
* Toxicity grading taken from FDA guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials [FDA, 2007].
** 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.

In order to determine the grading, the following rules will be used:

1. In case a conversion is needed, the original results will be used for the conversion without a previous rounding.
2. In case an approximation is needed to determine the grading, the result (or the result divided by the ULN range, depending on the test) expressed in the expected unit will be rounded to the number of decimals used for the grading.

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

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., EKG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

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

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

g. Other situations:

- Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Solicited events

- **Definition of solicited event**
- Solicited events are predefined events administration site events and systemic events for which the participant is specifically questioned, and which are noted by the participant in their eDiary.

a. Solicited administration site events

The following administration site events will be solicited:

Table 21 Solicited administration site events

Pain at administration site
Redness at administration site
Swelling at administration site
Lymphadenopathy (Axillary swelling/ tenderness ipsilateral to the site of injection)

b. Solicited systemic events

The following systemic events will be solicited:

Table 22 Solicited systemic events

Fever
Headache
Myalgia (muscle pain)
Arthralgia (joint pain)
Fatigue (tiredness)
Chills
Abdominal pain
Vomiting
Diarrhea

Note: Participants 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 will be instructed to record the highest temperature in the eDiary.

10.3.4. Unsolicited AE

Definition of unsolicited AE
• An unsolicited AE is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by participants who signed the informed consent. Unsolicited AEs include both serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants 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 concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. Recording, assessment and follow-up of AE, SAE, AESIs and pregnancies

10.3.5.1. AE, SAE and AESI recording

- When an AE/SAE/AESI occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/AESI information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to CRO in lieu of completion of the eCRF/required form.
- There may be instances when copies of medical records for certain cases are requested by CRO. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to CRO.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- An eDiary will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete the eDiary.
- Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record.

- For each solicited and unsolicited AE the participant experiences, the participant will be asked if they received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's eDiary (for solicited AEs) and in the participant's eCRF as part of normal AE reporting (for unsolicited AEs). If the collection of solicited AEs was not possible for any reasons via the eDiary and solicited AEs were reported to the investigator by the participant, then it would be possible for it to be reported directly to the site staff and submitted (e.g. via the eCRF). Medical attention received for SAEs/AESIs will have to be reported using the normal AE reporting process in the eCRF.
- Any unreturned eDiary will be sought from the participant through telephone call(s) or any other convenient procedure.

10.3.5.2. Assessment of intensity

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

- Mild:

  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:

  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:

  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Table 23 Intensity scales for solicited events

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities
	2	Moderate: Painful when limb is moved and interferes with everyday activities
	3	Severe: Significant pain at rest. Prevents normal everyday activities
Redness at administration site	0	Greatest surface diameter < 25 mm
	1	Greatest surface diameter 25 - 50 mm
	2	Greatest surface diameter 51 - 100 mm
	3	Greatest surface diameter > 100 mm
Swelling at administration site	0	Greatest surface diameter < 25 mm
	1	Greatest surface diameter 25 - 50 mm
	2	Greatest surface diameter 51 - 100 mm
	3	Greatest surface diameter > 100 mm
Temperature*	0	< 38.0°C (100.4°F)
	1	38.0°C (100.4°F) - 38.4°C (101.1°F)
	2	38.5°C (101.2°F) - 38.9°C (102.0°F)
	3	>38.9°C (102.0°F)
Arthralgia (joint pain)	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	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue (tiredness)	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Lymphadenopathy	0	None
	1	Mild: No interference with activity
	2	Moderate: Some interference with daily activity or requires repeated use of non-narcotic pain reliever
	3	Severe: Prevents daily activity or requires use of narcotic pain reliever
Chills	0	None
	1	Mild sensation of cold; shivering; chattering of teeth
	2	Moderate tremor of the entire body; narcotics indicated
	3	Severe or prolonged, not responsive to narcotics
Myalgia (muscle pain)	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
Abdominal pain	0	Normal
	1	Mild: No interference with daily activity
	2	Moderate: Interferes with daily activity
	3	Severe: Prevents daily activity

Event	Intensity grade	Parameter
Vomiting	0	None
	1	Mild: No interference with activity or 1-2 episodes/24 hours
	2	Moderate: Some interference with activity or >2 episodes in 24 hours
	3	Severe: Prevents daily activity, requires outpatient intravenous hydration
Diarrhea	0	None
	1	Mild: 2-3 loose stools or <400g in 24 hours
	2	Moderate: 4-5 stools or 400-800 g in 24 hours
	3	Severe: 6 or more water stools or >800g in 24 hours or requires outpatient intravenous hydration

* Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.

10.3.5.3. Assessment of causality

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

10.3.5.4. Assessment of outcomes

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

- Recovered/resolved
- Recovering/resolving

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

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

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

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

Other nonserious AEs be followed until the participant is lost to follow-up.

Follow-up during the study

AEs/AESIs **documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until** the end of the study or the participant is lost to follow-up.

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

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

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

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

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.5.7. Reporting of SAEs, AESIs and pregnancies

SAE Reporting to CRO via an Electronic Data Collection Tool

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

SAE Reporting to CRO via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the CRO medical monitor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.7.

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

10.4.1. Definitions

10.4.1.1. WOCBP

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

10.4.1.1.1. Women not considered as WOCBP (WONCBPs)

- 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

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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement >40 IU/L (or mIU/mL) is required.

- 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 enrollment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 24).

Table 24 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] ***Failure rate of <1% per year when used consistently and correctly.***
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable • Oral (if allowed by local regulation or if it is part of standard medical practice in the country).
Highly effective methods that are user independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilization prior to the female participant's entry into the 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.)*

10.5. Appendix 5: Protocol amendment history

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

Amendment 2

Overall Rationale for the Amendment:

The Protocol Amendment 2 has been amended to align with the updated guidance released by the FDA on "*Development and Licensure of Vaccines to Prevent COVID-19*". In this guidance, the FDA indicated that safety monitoring longer than 6 months will only be "warranted for certain vaccine platforms (e.g., those that include novel adjuvants)". Hence, the follow-up of participants has been reduced from 12 months to 6 months.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 (Schema), Table 1 (SoA), Table 3 (Study objectives, endpoints and estimands), Section 4.1 (Overall design), Section 4.4 (End-of-study definition), Section 8.2 (Immunogenicity assessments), Table 7 (Biological samples), Table 9 (Immunological read-outs), Section 8.4.1 (Time period and frequency for collecting AE, SAE and other safety information), Table 11 (Timeframes for collecting and reporting of safety information), Section 9.4.2.1 (Safety endpoints), Section 9.5.1 (Sequence of analyses)	Participant follow-up was reduced from 12 months to 6 months (i.e., study concludes at Visit 5 in Month 6 instead of Visit 6 in Month 12).	To align with updated FDA guidance and facilitate assessments and visits for study participants
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS Section 10.1.3 (Informed consent process)	Deleted "Legally authorized representative" and "LAR".	"Legally authorized representative" is not applicable for this study since all participants are adults.
Table 1 (SoA)	Under "Unscheduled COVID-19" column, Medical History, Physical examination, Vital signs measurement, and Body temperature were added as study procedures requiring documentation in the individual eCRF.	To align with protocol text in Section 8.4.4.2.2.
Section 9.4.1	Deleted "and any antipyretic taken prophylactically"	This is analysed descriptively from the Concomitant Medication eCRF.
Section 11 (References)	Included the reference to the guidance released by the FDA on "Development and Licensure of Vaccines to Prevent COVID-19".	This guidance serves as the basis for the amendment described above; hence, it has been included as a reference.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore not summarized.

Amendment 1

Overall Rationale for the Amendment

The Protocol Amendment 1 has been amended to comply with CBER requests, to provide clarification, to remove unnecessary restrictions, and to correct errors in the original protocol.

Summary of changes table of previous amendments:

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor; therefore, not summarized
Title Page	Change in Sponsor Signatory; IND number was added	GSK Signatory has been changed to reflect the current Sponsor Signatory; IND number was added once available.
List of Abbreviations	FAS (Full Analysis Set) was removed	FAS is no longer in the protocol
Definition of Terms	The terms Adverse Event, Adverse Drug Reaction, Auxiliary Medicinal Product (AxMP), Background treatment, Challenge agents, Co-administered (concomitant) products, Comparator, Investigational Product, Medicinal products used to assess end-points, Placebo, Rescue medications, Standard of Care, and SUSAR were added	These terms were added for compliance reasons
Section 1.1 (Synopsis), Section 1.2 (Schema); Section 4.1 (Overall design)	"multicenter" was added	To comply with a CBER request
Section 2.1 (Study rationale), Section 5.1 (Inclusion criteria)	"the booster administered between 6 and 18 months prior to screening" was changed to "the last booster dose administered at least 6 months or more prior to screening"	To remove this unnecessary restriction in the original protocol
Section 2.2 (Background)	"ongoing COVID-19 pandemic" was replaced with "ongoing impact of COVID-19"	Since the pandemic is officially over
Table 3 (Study objectives, endpoints, and estimands)	"30" was changed to "29"; "GMTs" was changed to "GMCs"; "M6" was changed to "study conclusion"; "titers" was changed to "concentrations"; "M12" was added to the third tertiary endpoint;	To correct errors
Section 4.1 (Overall design)	"The study will be conducted in the United States (US)" was added	To comply with a CBER request
Table 4 (Study groups, intervention, and blinding)	"TC: Telephone call" was deleted from the table caption	"TC" was not present in the table
Section 6.3.4 (Blinding and unblinding)	"efficacy" was replaced with "immunogenicity"	To correct an error

Section # and Name	Description of Change	Brief Rationale
Table 15 (Analysis sets)	"Full analysis" and "Unsolicited safety" were deleted	These are not applicable to planned analyses for this study (refer to Section 9.4 for details)
Table 15 (Analysis sets)	"D15 neutralizing titers against pseudovirus bearing S protein from the Omicron variant of SARS-CoV-2" was replaced with "post-dose specified immunogenicity data for the relevant timepoint"; In the Solicited Safety section, "reported the presence or absence of any" was added, and "safety data" was replaced with "AE at least once"	To provide clarification
Table 15 (Analysis sets)	In the Overall Safety section, "Unsolicited" was replaced with "Exposed"	To be consistent with planned analyses
Section 9.4.1 (Primary endpoint)	"Exposed Set, except for solicited AEs, which will be performed on the" was added; "and the Unsolicited Safety Set" was deleted;	To be consistent with planned analyses
Section 9.4.1 (Primary endpoint)	"screening" was replaced with "Day 1, or if not available, closest visit available to D1 before IMP administration	To correct an error
Section 9.4.2.2 (Immunogenicity endpoints)	"FAS" was replaced with "Exposed Set"; "and binding IgG Ab" was removed; "GMCs/" was removed; "number of doses received pre-Day 1 and time from last dose" was replaced with "treatment group"	To be consistent with planned analyses
Table 16 (Protocol required safety laboratory assessments)	"Prothrombin Time / INR" was added	This safety lab was inadvertently missed in this Table in the original protocol, even though INR had been noted in the footnote
Table 18 (Toxicity grading scales for hematology parameters evaluated in the current study)	"Prothrombin Time – increase by factor," "1.03 – 1.10 x ULN," "1.11 – 1.20 x ULN," "1.21 – 1.25 x ULN," and ">1.25 x ULN" were added	This safety lab (i.e., Prothrombin Time) was inadvertently missed in this Table in the original protocol

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