# Clinical Study Protocol

| | |
|---|---|
| **Primary Study Interventions** | CV0701 mRNA vaccine<br>CV0601 mRNA vaccine<br>***CV0801 mRNA vaccine*** |
| **Other Study Intervention** | CCI [redacted]<br>CCI [redacted] |
| **Study Identifier** | 219075 (CV2 SARS-COV2-013 BST) |
| **EU CT Number** | 2023-504596-25-00 |
| **Approval date** | 26 Sep 2023 |
| **Title** | A Phase 2 randomized, active-controlled, observer-blind study to assess the safety, reactogenicity, and immunogenicity of a booster dose of investigational COVID-19 mRNA vaccines in healthy adults who previously received a complete primary vaccination series with or without booster dose(s) |
| **Brief Title** | A study on the safety, reactogenicity, and immune response of a booster dose of investigational COVID-19 mRNA vaccines in healthy adults |
| **Sponsor** | GlaxoSmithKline Biologicals S.A.<br>Rue De L'Institut 89<br>1330 Rixensart<br>Belgium |
| **Sponsor Signatory** | Martin Gaudinski<br>Clinical Project Lead |

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

# *PROTOCOL AMENDMENT 1 INVESTIGATOR AGREEMENT*

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical study agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- 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 on-site or elsewhere without the approval of GSK and the express 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 and data management processes of the study with respect to data entry and 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 study 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.

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|---|---|
| **Study identifier** | 219075 (CV2 SARS-COV2-013 BST) |
| **EU CT Number** | 2023-504596-25-00 |
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| **Title** | A Phase 2 randomized, active-controlled, observer-blind study to assess the safety, reactogenicity, and immunogenicity of a booster dose of investigational COVID-19 mRNA vaccines in healthy adults who previously received a complete primary vaccination series with or without booster dose(s) |

**Investigator name** _____

**Signature** _____

**Date of signature**

(DD Month YYYY) _____

PPD
**name, function and title** _____

**Signature** _____

**Date of signature**

(DD Month YYYY) _____

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date of Issue** |
| ***Amendment 1*** | 26 Sep 2023 |
| ***Original Protocol*** | ***04 May 2023*** |

***Amendment 1 (***26 Sep 2023***)***

***This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.***

**Overall rationale for the current Amendment:**

***The objective of this amendment is to add a Part B to this Phase 2 study to provide exploratory safety and immunogenicity evidence of non-inferiority to our investigational vaccine stored at different conditions. The ongoing study described in the Protocol will herein be defined as Part A.***

## List of main changes in the protocol and their rationale:

| Section # and title | Description of change | Brief rationale |
|---|---|---|
| ***Title page; Study interventions*** | ***The study intervention, "CV0801", was added to the list of study intervention.*** | ***To include the study intervention used for Phase 2 Part B.*** |
| ***1.2. Schema*** | ***A schema was added for the Part B study design.*** | ***To summarize all the aspects of Part B design.*** |
| ***1.3. Schedule of activities*** | ***A new SoA for Part B participants has been developed.*** | ***To ensure all protocol-mandated procedures of Part B are detailed.*** |
| ***2.2. Study rationale*** | ***The Part B study rationale has been added as a subsection.*** | ***To explain the objective of Phase 2 Part B study.*** |
| ***2.3. Benefit/risk assessment*** | ***The study intervention CV0801 was added.*** | ***To ensure the benefit/risk assessment is aligned with both Part A and Part B of the protocol.*** |
| ***3. Objectives, endpoints, and estimands*** | ***The immunogenecity and safety primary objectives and endpoints for Phase 2 Part B have been added in a separate table.*** | ***To ensure both Part A and Part B objectives and endpoints are reported.*** |

| Section # and title | Description of change | Brief rationale |
|---|---|---|
| ***4.1. Overall study design*** | ***The overall study design section has been divided in 2 subsections to describe Part A and Part B specific study design aspects.*** | ***To ensure that the specificity of the study design is clearly explained for Part A and Part B.*** |
| ***4.2 Scientific rationale for study design*** | ***The section has been divided into 2 subsections to describe Part A and Part B specific scientific rational aspects.*** | ***To ensure that the specificity of the scientific rationale for study design is clearly explained for Part A and Part B.*** |
| ***4.3. Justification of dose*** | ***A rationale was provided for the choice of the CV0801 dose, as well as the objective for using alternative storage conditions.*** | ***To explain why the dose and storage conditions chosen are important for the Part B study rationale.*** |
| ***5.2 Exclusion criteria*** | ***A new exclusion criterium has been added.*** | ***To clarify that participants to Part A cannot be enrolled in Part B.*** |
| ***6.1. Study interventions administered*** | ***A table has been added to describe the study interventions administered to Part B participants.*** | ***To ensure a detailed description of the Part B study interventions is included in the protocol.*** |
| ***8 Study assessments and procedures and Section 8.2. Immunogenicity assessments*** | ***Overall blood volumes that will be collected from each participant have been specified for Part A and Part B participants. Part B immunogenicity assessments have also been added in the relevant tables: biological samples, laboratory assays, and immunological reads-out. The tables have been modified to show Part A and Part B relevant information.*** | ***To ensure clarity of the immunogenicity assessments that are to be performed in Part A and Part B .*** |

| Section # and title | Description of change | Brief rationale |
|---|---|---|
| ***8.5 Committees structure*** | ***Details about Part B have been added*** | ***To explain frequency of committee review for both Part A and Part B.*** |
| ***9 Statistical considerations*** | ***Statistical information relevant to Part B has been added. The number of participants to be enrolled in Part B and the ratio of their distribution in the 3 groups of this Phase 2 study was provided.*** | ***To ensure preliminary evidence of non-inferiority between the different conditions can be provided with Part B of the study.*** |
| ***9.4 Interim analysis*** | ***Details about aggregate summaries have been added.*** | ***To ensure the sharing of aggregate data to the SRT to assist with Regulatory interactions*** |
| ***9.5 Sample size determination*** | ***Details on Part B have been added.*** | ***To define how sample size will be determined for Part A and Part B.*** |

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| **Ab** | Antibody |
| **AE** | Adverse event |
| **AESI** | Adverse event of special interest |
| **ANCOVA** | Analysis of covariance |
| **CI** | Confidence interval |
| CCI | |
| **COVID-19** | Coronavirus disease 2019 |
| **CRO** | Contract research organization |
| **CV0601** | Monovalent modified-nucleoside LNP encapsulated mRNA COVID-19 vaccine candidate encoding the CCI CCI spike proteins of the CCI variants |
| **CV0701** | Bivalent modified-nucleoside LNP encapsulated mRNA COVID-19 vaccine candidate encoding the CCI strain spike and CCI spike proteins |
| **CV0801** | Monovalent modified-nucleoside LNP encapsulated mRNA COVID-19 vaccine encoding the CCI spike protein with the CCI |
| **ECG** | Electrocardiogram |
| **eCRF** | Electronic case report form |
| **eDiary** | Electronic diary |
| **EMA** | European Medicines Agency |
| **EoS** | End-of-study |
| **EoSL** | End of shelf life |
| **ES** | Exposed Set |
| **FDA** | Food and Drug Administration |
| **FSH** | Follicule-stimulating hormone |

| Abbreviation | Definition |
|---|---|
| **GCP** | Good Clinical Practice |
| **GMF** | Geometric mean frequency |
| **GMI** | Geometric mean increase |
| **GMT** | Geometric mean titer |
| **GSK** | GlaxoSmithKline Biologicals S.A. |
| **HRT** | Hormonal replacement therapy |
| **IB** | Investigator's brochure |
| **ICF** | Informed consent form |
| **ICH** | International Council on Harmonisation |
| **IDMC** | Independent data monitoring committee |
| **iDRC** | Internal data review committee |
| **IEC** | Independent ethics committee |
| **IgG** | Immunoglobulin G |
| **IMP** | Investigational medicinal product |
| **IRB** | Institutional review board |
| **LLOQ** | Lower limit of quantification |
| **LNP** | Lipid nanoparticle |
| **LPLV** | Last Participant Last Visit |
| **MAAE** | Medically attended adverse event |
| **modRNA** | Nucleoside-modified messenger RNA |
| **mRNA** | Messenger ribonucleic acid |
| CCI [redacted] | |
| **pIMD** | Potential immune-mediated disease |

| Abbreviation | Definition |
|---|---|
| CCI [redacted] | |
| **PT** | Preferred term |
| **QTL** | Quality tolerance limit |
| **RT-PCR** | Reverse transcription 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 |
| **SRT** | Safety Review Team |
| **ULN** | Upper limit of normal |
| **US** | United States |
| **VRBPAC** | Vaccines and Related Biological Products Advisory Committee |
| **WHO** | World Health Organization |
| **WOCBP** | Women of childbearing potential |

| Term | Definition |
|---|---|
| **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.<br>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).<br>b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized |

| Term | Definition |
|---|---|
| **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. Authorised 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.<br>1. 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<br>1. Safety reporting for unauthorised 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 an SAE.<br>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. |

| Term | Definition |
|---|---|
| **Certified copy** | A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. |
| **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 participant 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. |
| **Essential documents** | Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. |
| **Intervention number** | A number identifying an intervention to a participant, according to intervention allocation. |
| **Investigational medicinal/vaccine product** | An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, 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. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met. |

| Term | Definition |
|---|---|
| **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 authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. |
| **Investigator** | A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.<br>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).<br>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. |
| **Primary completion date** | The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure.<br>Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures. |
| **Randomization** | Process of random attribution of intervention to participants to reduce selection bias. |

| Term | Definition |
|---|---|
| **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. |
| **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). |
| **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.<br>1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries |
| **Study completion date** | The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LPLV). |
| **Study 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.<br>Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified. |
| **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. |

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Protocol Title:** A Phase 2 randomized, active-controlled, observer-blind study to assess the safety, reactogenicity, and immunogenicity of a booster dose of investigational COVID-19 mRNA vaccines in healthy adults who previously received a complete primary vaccination series with or without booster dose(s).

**Brief Title:** A study on the safety, reactogenicity, and immune response of a booster dose of investigational COVID-19 mRNA vaccines in healthy adults.

**Rationale:** Refer to Section 2.2.

**Objectives, Endpoints, and Estimands:** Refer to Section 3.

**Overall Design:** Refer to Section 4.1.

**Number of Participants:** Refer to Section 9.5.

**Data Monitoring/Other Committee:** Refer to Section 8.5.

## 1.2. Schema

**Figure 1** ***Part A:*** **Study design overview**

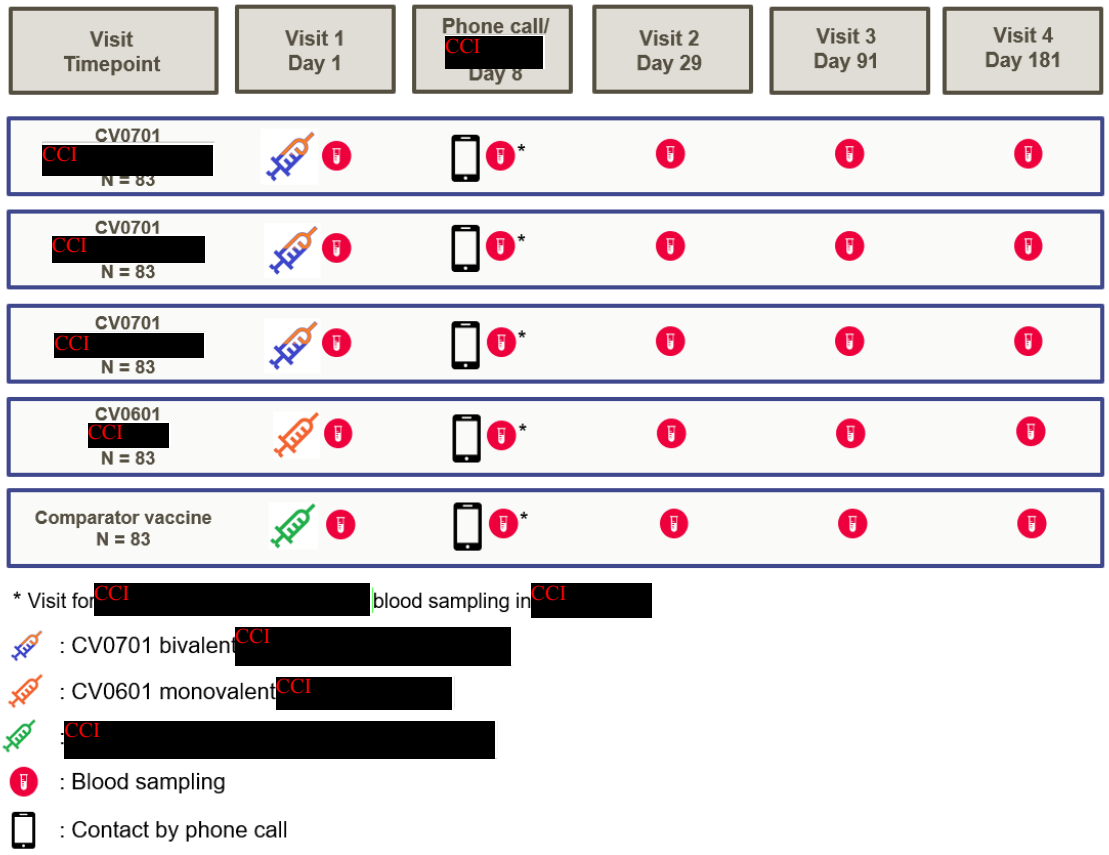
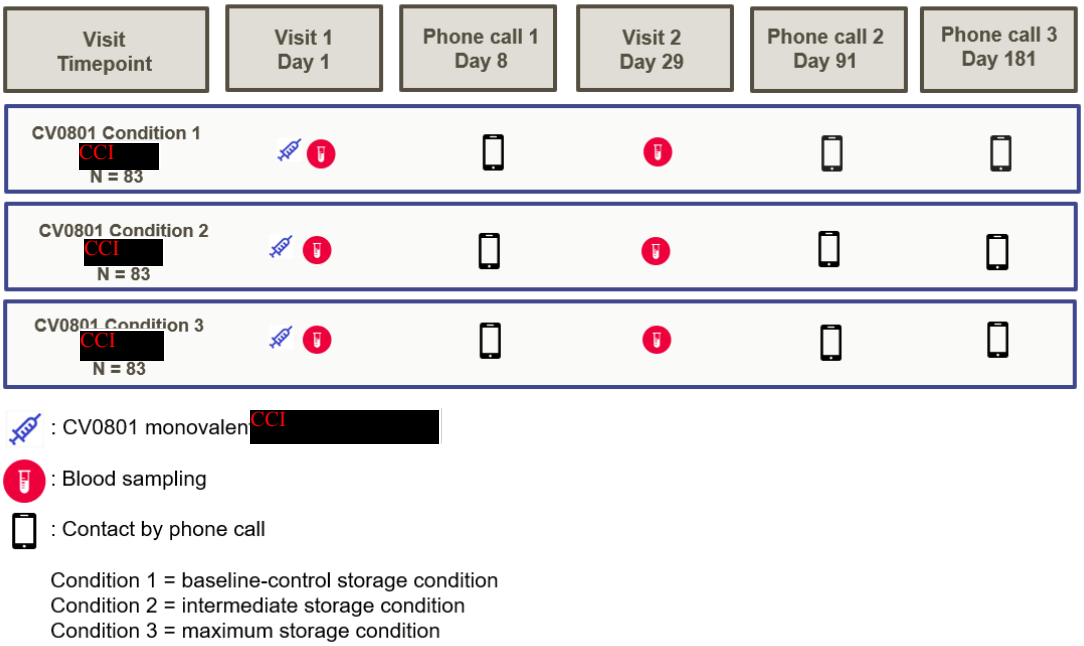


**Figure 2** ***Part B: Study design overview***



## 1.3. Schedule of Activities

### Table 1 Schedule of activities *for Part A*

| | Day 1 | Day 8 Phone Call/ Visit[b] | Day 29 | Day 91 | Day 181 (EoS) | Unscheduled Visit[c] | ET Visit | Notes |
|---|---|---|---|---|---|---|---|---|
| **Window (days)** | **0[a]** | **±1** | **±3** | **±7** | **±7** | | | |
| **Visit** | **1** | CCI | **2** | **3** | **4** | | | |
| Informed consent | X | | | | | | | See Section 10.1.3 for details |
| Distribution of participant card | X | | | | | | | See Section 8.4.8 for details |
| Inclusion/exclusion assessment | X | | | | | | | See Sections 5.1 and 5.2 for inclusion and exclusion criteria |
| Demographics | X | | | | | | | See Section 8.1.1 for more information |
| Medical history (including vaccination history) | X | | | | | X[d] | | See Section 8.1.2 for more information |
| Concomitant medication/vaccination | X | X | X | X | X | X | X | See Section 6.9 for more information |
| Vital sign measurements[e] | X | | | | | X | | See Section 8.3.2 for more information |
| Physical examination[f] | X | | X | X | X | X | X | See Section 8.3.1 for more information |
| Pregnancy test[g] | X | | | | | | | See Section 8.3.3 for more information |
| Blood sample for immunogenicity CCI CCI and, if needed, for eligibility assessment (~56 mL)[h] | X | | X | X | X | | | See Section 8.2 for more information |
| CCI CCI | X | X[b] | | | | | | See Section 8.2 for more information |
| SARS-CoV-2 anti-nucleocapsid antibody serology | X[i] | | X | X | X | | | See Section 8.2 for more information |
| SARS-CoV-2 RT-PCR (swab) | X[j] | | | | | X | | See Section 8.4.4.2 for more information |
| Randomization | X | | | | | | | See Section 6.3 for more information |
| Study intervention administration (including 30-minute post-vaccination observation) | X | | | | | | | See Section 6.1 for more informatio |
| Initiate eDiary for solicited AEs | X | | | | | | | See Section 10.3.6 for more information |
| Site staff review of eDiary | | X | | | | | | See Section 10.3.6 for more information |
| Return of the eDiary device | | | X | | | | | See Section 10.3.6 for more information |
| Recording of AESIs, MAAEs, and SAEs | X | X | X | X | X | X | X | See Section 10.3.6 for more information |

| | Day 1 | Day 8 Phone Call/ Visit[b] | Day 29 | Day 91 | Day 181 (EoS) | Unscheduled Visit[c] | ET Visit | Notes |
|---|---|---|---|---|---|---|---|---|
| **Window (days)** | **0[a]** | **±1** | **±3** | **±7** | **±7** | | | |
| **Visit** | **1** | CCI | **2** | **3** | **4** | | | |
| Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[k] | X | X | X | X | X | X | X | See Section 10.3.6 for more information |
| Recording of unsolicited AEs | X | X | X | | | X[l] | | See Section 10.3.6 for more information |
| Participant study completion | | | | | X | | | See Section 4.4 for EoS definition |

AE: adverse event; AESI: adverse events of special interest; CCI; EoS: end-of-study; ET: early termination; IgG: immunoglobulin G; MAAE: medically attended adverse event; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
Of note, safety follow-up may be completed via an unscheduled visit as permitted by country regulations.

a. If a protocol-related procedure needs to be conducted to confirm eligibility or if the participant is likely to fulfill the eligibility criteria after a period of delay, the study intervention administration may be postponed up to a maximum of 14 days until the result is obtained and/or eligibility can be confirmed (refer to Section 5.5 for details).
b. Additional planned visit only for participants in CCI
c. In case of acute COVID-19 assessment, the unscheduled visit may be used to collect a SARS-CoV-2 swab for RT-PCR testing. Participants will be asked to contact the site immediately should they experience any symptoms of COVID-19, myocarditis, or pericarditis, and an unscheduled visit may be performed.
d. Evaluation and review of present COVID-19 illness history of the participants, including medical records to define the severity of COVID-19.
e. Vital sign measurements (temperature, pulse rate, respiration rate, and blood pressure) should be collected before and after study intervention administration on Day 1.
f. A complete physical examination including height and weight will be performed on Day 1 prior to study intervention administration. Only symptom-directed physical examinations will be performed if clinically indicated at subsequent visits.
g. A urine pregnancy test will be performed on Day 1 for female participants of childbearing potential. Negative confirmation is required prior to study intervention administration.
h. Other analyses, such as serum FSH to confirm postmenopausal status, may be performed if required.
i. Randomization and study intervention administration may proceed before the anti-nucleocapsid antibody results are available.
j. A SARS-CoV-2 swab for RT-PCR testing should be obtained at Day 1 to establish baseline characteristics. Randomization and study intervention administration may proceed before the results are available.
k. SAEs related to study participation, or to a concurrent GSK medication/vaccine, should be collected from the time that informed consent is obtained (prior to study intervention administration) until the participant is discharged from the study.
l. Unsolicited AEs will only be collected if the unscheduled visit occurs within Days 1 through 28 after vaccination.

## *Table 2 Schedule of activities for Part B*

| | Day 1 | Day 8 | Day 29 | Day 91 | Day 181 (EoS) | Unscheduled Visit[b] | ET Visit | Notes |
|---|---|---|---|---|---|---|---|---|
| Window (days) | 0[a] | ±1 | ±3 | ±14 | ±14 | | | |
| Visit | 1 | Phone Call 1 | 2 | Phone Call 2 | Phone Call 3 | | | |
| Informed consent | X | | | | | | | See Section 10.1.3 for details |
| Distribution of participant card | X | | | | | | | See Section 8.4.8 for details |
| Inclusion/exclusion assessment | X | | | | | | | See Sections 5.1 and 5.2 for inclusion and exclusion criteria |
| Demographics | X | | | | | | | See Section 8.1.1 for more information |
| Medical history (including vaccination history) | X | | | | | X[c] | | See Section 8.1.2 for more information |
| Concomitant medication/vaccination | X | X | X | X | X | X | X | See Section 6.9 for more information |
| Vital sign measurements[d] | X | | | | | X | | See Section 8.3.2 for more information |
| Physical examination[e] | X | | X | | | X | X | See Section 8.3.1 for more information |
| Pregnancy test[f] | X | | | | | | | See Section 8.3.3 for more information |
| Blood sample for immunogenicity (neutralizing titers) and, if needed, for eligibility assessment (~20 mL)[g] | X | | X | | | | | See Section 8.2 for more information |
| SARS-CoV-2 anti-nucleocapsid antibody serology | X[h] | | X | | | | | See Section 8.2 for more information |
| SARS-CoV-2 RT-PCR (swab) | X[i] | | | | | X | | See Section 8.4.4.2 for more information |
| Randomization | X | | | | | | | See Section 6.3 for more information |
| Study intervention administration (including 30-minute post-vaccination observation) | X | | | | | | | See Section 6.1 for more informatio |
| Initiate eDiary for solicited AEs | X | | | | | | | See Section 10.3.6 for more information |
| Site staff review of eDiary | | X | | | | | | See Section 10.3.6 for more information |
| Return of the eDiary device | | | X | | | | | See Section 10.3.6 for more information |
| Recording of AESIs, MAAEs, and SAEs | X | X | X | X | X | X | X | See Section 10.3.6 for more information |
| Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[j] | X | X | X | X | X | X | X | See Section 10.3.6 for more information |
| Recording of unsolicited AEs | X | X | X | | | X[k] | | See Section 10.3.6 for more information |
| Participant study completion | | | | | X | | | See Section 4.4 for EoS definition |

***AE: adverse event; AESI: adverse events of special interest; EoS: end-of-study; ET: early termination; MAAE: medically attended adverse event; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2***
***Of note, safety follow-up may be completed via an unscheduled visit as permitted by country regulations.***

- ***a. If a protocol-related procedure needs to be conducted to confirm eligibility or if the participant is likely to fulfill the eligibility criteria after a period of delay, the study intervention administration may be postponed up to a maximum of 14 days until the result is obtained and/or eligibility can be confirmed.***
- ***b. In case of acute COVID-19 assessment, the unscheduled visit may be used to collect a SARS-CoV-2 swab for RT-PCR testing. Participants will be asked to contact the site immediately should they experience any symptoms of COVID-19, myocarditis, or pericarditis, and an unscheduled visit may be performed.***
- ***c. Evaluation and review of present COVID-19 illness history of the participants, including medical records to define the severity of COVID-19.***
- ***d. Vital sign measurements (temperature, pulse rate, respiration rate, and blood pressure) should be collected before and after study intervention administration on Day 1.***
- ***e. A complete physical examination including height and weight will be performed on Day 1 prior to study intervention administration. Only symptom-directed physical examinations will be performed if clinically indicated at subsequent visits.***
- ***f. A urine pregnancy test will be performed on Day 1 for female participants of childbearing potential. Negative confirmation is required prior to study intervention administration.***
- ***g. Other analyses, such as serum FSH to confirm postmenopausal status, may be performed if required.***
- ***h. Randomization and study intervention administration may proceed before the anti-nucleocapsid antibody results are available.***
- ***i. A SARS-CoV-2 swab for RT-PCR testing should be obtained at Day 1 to establish baseline characteristics. Randomization and study intervention administration may proceed before the results are available.***
- ***j. SAEs related to study participation, or to a concurrent GSK medication/vaccine, should be collected from the time that informed consent is obtained (prior to study intervention administration) until the participant is discharged from the study.***
- ***k. Unsolicited AEs will only be collected if the unscheduled visit occurs within Days 1 through 28 after vaccination.***

**Table 3 Intervals between study visits *for Part A***

| Interval | Planned visit interval | Allowed interval range |
|---|---|---|
| Visit 1 (Day 1)→Phone call / CCI CCI (Day 8) | 7 days | 7±1 ***day*** |
| Visit 1 (Day 1)→Visit 2 (Day 29) | 28 days | 28±3 ***days*** |
| Visit 1 (Day 1)→Visit 3 (Day 91) | 90 days | 90±7 ***days*** |
| Visit 1 (Day 1)→Visit 4 (Day 181) | 180 days | 180±7 ***days*** |

If the study intervention date is different from the ICF signature date, the study intervention date needs to be taken as a reference for calculating intervals relative to subsequent visits.
Interval is computed as the difference between 2 dates.

***Table 4 Intervals between study visits for Part B***

| *Interval* | *Planned visit interval* | *Allowed interval range* |
|---|---|---|
| ***Visit 1 (Day 1)→Phone call 1 (Day 8)*** | ***7 days*** | ***7±1 day*** |
| ***Visit 1 (Day 1)→Visit 2 (Day 29)*** | ***28 days*** | ***28±3 days*** |
| ***Visit 1 (Day 1)→Phone call 2 (Day 91)*** | ***90 days*** | ***90±14 days*** |
| ***Visit 1 (Day 1)→Phone call 3 (Day 181)*** | ***180 days*** | ***180±14 days*** |

***If the study intervention date is different from the ICF signature date, the study intervention date needs to be taken as a reference for calculating intervals relative to subsequent visits.***
***Interval is computed as the difference between 2 dates.***

# 2. INTRODUCTION

## 2.1. Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 [WHO, 2020]. As of 9 February 2023, more than 755 million cases have been reported worldwide, leading to more than 6.8 million deaths [WHO, 2023], although this is likely to be substantial underestimate of the true burden of disease [WHO, 2021a]. On 30 January 2023, the WHO Director-General concurred that the ongoing COVID-19 pandemic continues to constitute a public health emergency of international concern [WHO, 2023].

By December 2020, the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) authorized the first vaccines containing Ancestral strain spike proteins. Since then, the emergence of SARS-CoV-2 variants (e.g., Delta and Omicron) that have the potential to escape immunity conferred by the originally approved vaccines prompted the need for continued development of COVID-19 mRNA vaccines to provide protection against circulating variants of concern [Garcia-Beltran, 2021; Zhou, 2021]. Accumulating real world data substantiate both the protective benefits of mRNA COVID-19 vaccines over non-mRNA vaccines [Self, 2021], and the need for additional doses beyond the primary series due to waning immunity. At least 126 countries worldwide have issued recommendations on booster or additional vaccinations [WHO, 2021b].

In partnership with CureVac AG, GlaxoSmithKline Biologicals S.A. (GSK) developed CV0501, a monovalent modified-nucleoside mRNA COVID-19 vaccine encoding the CCI spike protein, which was a circulating variant of concern [CDC, 2023]. The Phase 1 study for CV0501, study 218595 (CV2 SARS-COV2-012 BST), entitled *"A Phase 1, Open-label, Safety and Immunogenicity Study of a Booster Dose of the Investigational CV0501 mRNA COVID-19 Vaccine in Adults at Least 18 Years Old"* is currently ongoing and its interim analyses provided the basis for the design of this Phase 2 study.

In June 2022, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommended that COVID-19 vaccine strain composition be updated to include the dominant circulating variant of concern, Omicron BA.4-5 [Marks, 2022]. Subsequently, Moderna and Pfizer-BioNTech obtained authorization for their bivalent formulations to be used as a single booster dose in select populations [FDA, 2022].

Due to the June 2022 VRBPAC recommendation to change from monovalent to bivalent COVID-19 booster vaccination, CureVac and GSK have developed CV0701, a bivalent modified-nucleoside mRNA COVID-19 vaccine encoding the CCI and CCI. It is an admix of 2 monovalent modified-nucleoside mRNA COVID-19 vaccines; CV0601 CCI ) and CV0801 CCI CCI . CCI CCI CCI The vaccines are intended to be administered intramuscularly as a single booster dose for prevention of COVID-19 caused by SARS-CoV-2.

## *2.2.* Study rationale

### *2.2.1.* *Study rationale for Part A*

***Within this Phase 2 study***, the purpose of ***Part A*** is to evaluate the safety, reactogenicity and immunogenicity of CV0701 and CV0601 ***in*** healthy adults who have previously received a complete primary vaccination series with or without booster dose(s). By including both bivalent and monovalent vaccine candidates, the study will also provide information on possible immune interference between the CCI and CCI spike protein antigens encoded in the bivalent vaccine (CV0701), compared with the CCI spike protein antigen solely encoded in the monovalent vaccine (CV0601).Within the study, CV0701 and CV0601 will be compared to CCI CCI in a randomized observer-blinded fashion.

### *2.2.2.* *Study rationale for Part B*

***The purpose of Part B is to evaluate the safety and Day 29 immunogenicity of CV0801 under 3 different storage conditions.***

## 2.3. Benefit/risk assessment

### 2.3.1. Risk assessment

Detailed information about the known and expected risks of the CV0601, CV0701, ***and CV0801*** vaccines is provided in the Investigator's Brochure (IB). Important potential risks are the following:

- Hypersensitivity reactions, including anaphylaxis
- Myocarditis
- Pericarditis

To mitigate these important potential risks, the following risk mitigation strategies have been included in the protocol:

- All participants will remain under observation at the vaccination center for at least 30 minutes after vaccination.
- Individuals with history of hypersensitivity or severe allergic reaction to any previous mRNA vaccine or any component of the study intervention(s) are excluded from the study enrollment, and participants will be instructed to contact the study site immediately for occurrence of any possible hypersensitivity reaction within 1 day of vaccination.
- Individuals at increased risk of myocarditis or pericarditis and individuals with a history of myocarditis or pericarditis are excluded from the study enrollment. All participants will be educated on the symptoms of myocarditis and pericarditis and will receive guidance on contacting study personnel and seeking medical care if any of these symptoms occur. Any participants with suspected myocarditis or pericarditis within 6 weeks after study intervention administration will be referred to a cardiologist by the investigator for diagnosis and management. A safety follow-up will be ensured until resolution of symtpoms and/or abnormal test findings.
- Anaphylaxis or severe hypersensitivity within 24 hours after study intervention administration, myocarditis and pericarditis will be collected as adverse events of special interest (AESIs).
- Participants will receive close medical monitoring and medical assessments during the study per the Schedule of Activities (SoA) (Table 1 ***and Table 2***).

In addition, vasovagal syncope and other anxiety related reactions as a psychogenic response to the needle injection can occur following or even before any vaccination. Therefore, all participants will remain under observation at the vaccination center for at least 30 minutes after the vaccination.

The potential risks associated with the investigational vaccines are considered acceptable, considering the measures planned to minimize risk to participants in this study and experience from the Phase 1 study with CV0501, the monovalent modified-nucleoside mRNA vaccine encoding an CCI [redacted] spike protein using the CCI [redacted] as CV0601, CV0701, ***and CV0801*** (see Section 4.3).

***Whilst the June 2022 VRBPAC recommended a bivalent vaccine encoding the Original and*** CCI **,** a monovalent vaccine encoding the CCI CCI is also included in the original study (Part A) to evaluate specific scientific objectives that cannot be met with bivalent vaccines alone. It is not anticipated that the participants randomized to the monovalent vaccine cohort will be disadvantaged compared to their bivalent counterparts, and there is scientific equipoise between all groups.

Refer to the Prescribing Information or Summary of Product Characteristics for expected adverse reactions associated with CCI [Summary of product characteristics; Prescribing information].

### 2.3.2. Benefit assessment

Participants are not expected to directly benefit from study participation. However, their participation in this study will contribute to generating information regarding the safety and immunogenicity of the vaccine.

Additionally, study participants may benefit from gaining information about their general health status through the medical evaluations/assessments associated with this study (i.e., physical examination).

### 2.3.3. Overall benefit/risk conclusion

Considering the measures taken to minimize risk to participants in this study and given the accumulation of favorable safety/immunogenicity data from the Phase 1 study of CV0501 (see Section 4.3), the potential risks are justified by the anticipated benefits linked to the development of the investigational vaccines CV0601, CV0701***, and CV0801.***

# 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

**Table 5 Objectives and endpoints*for Part A***

| Primary Objectives | Primary Endpoints (population summary) |
|---|---|
| To compare the immunogenicity of CV0701 and CV0601 booster vaccines with CCI CCI at Day 29 | • Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (GMT)<br>• Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (GMT) |
| To evaluate the safety and reactogenicity of CV0701 and CV0601 booster vaccines | • Occurrence of solicited administration site and systemic AEs within 7 days (i.e., from Day 1 to Day 7 included) of study intervention administration (percentage of participants)<br>• Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28 included) of study intervention administration (percentage of participants)<br>• Occurrence of MAAEs, SAEs and AESIs from Day 1 through the end of the study (approximately 180 days after the study intervention administration), each summarized separately (percentage of participants) |
| **Secondary Objective** | **Secondary Endpoints (population summary)** |
| To compare the immunogenicity of CV0701 and CV0601 booster vaccines with CCI CCI CCI | • Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 91 and Day 181 (GMT)<br>• Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 91 and Day 181 (GMT)<br>• Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29, 91 and Day 181 (GMT)<br>• Seroresponse* from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (percentage of participants)<br>• Seroresponse* from baseline of serum neutralization titers against pseudovirus bearing specific CCI CCI spike protein at Day 29 (percentage of participants)<br>• Seroresponse* from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (percentage of participants)<br>• Fold increase from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29, Day 91, and Day 181 (GMI)<br>• Fold increase from baseline of serum neutralization titers against pseudovirus bearing specific CCI CCI spike protein at Day 29, Day 91, and Day 181 (GMI)<br>• Fold increase from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29, Day 91, and Day 181 (GMI) |

| | |
|---|---|
| CCI | [redacted] |

AE: adverse event; AESI: adverse events of special interest; GMI: geometric mean increase; GMT: geometric mean titer; IgG Ab: immunoglobulin G antibody; MAAE: medically attended adverse event; mRNA: messenger ribonucleic acid; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

* CCI [redacted]

CCI [redacted]

***Table 6 Objectives and endpointsfor Part B***

| *Primary Safety Objective* | *Primary Safety Endpoints (population summary)* |
|---|---|
| *To evaluate the safety and reactogenicity of three CV0801 booster vaccine manufacturing specifications* | *Solicited events:*<br>• *Occurrence of solicited administration site and systemic AEs within 7 days (i.e., from Day 1 to Day 7 included) of study intervention administration (percentage of participants)*<br>*Unsolicited events:*<br>• *Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28 included) of study intervention administration (percentage of participants)*<br>*SAEs, AESIs and MAAEs:*<br>• *Occurrence of MAAEs, SAEs and AESIs from Day 1 through the end of the study (approximately 180 days after the study intervention administration), each summarized separately (percentage of participants)* |
| *Primary Immunogenicity Objective* | *Primary Immunogenicity Endpoint* |
| *To evaluate the immunogenicity of three CV0801 booster vaccine manufacturing specifications* | • *Serum neutralization titers against pseudovirus bearing specific* CCI [redacted] *spike protein at Day 29 (GMT)* |

***AE: adverse event; AESI: adverse events of special interest; GMT: geometric mean titer; MAAE: medically attended adverse event; SAE: serious adverse event***

Complementary details on estimands such as impact of intercurrent events is provided in Section 9.

# 4. STUDY DESIGN

## 4.1. Overall design

### *4.1.1. Overall study design of Part A*

***Part A of the randomized,*** observer-blind Phase 2 study will evaluate the safety, reactogenicity and immunogenicity of a single booster dose of CV0701 and CV0601 compared to CCI [redacted] CCI [redacted] in healthy adults who have previously received a complete primary vaccination series with or without booster dose(s). Multiple dose strengths of CV0701 will be evaluated. Participants will be randomized equally across 5 arms, which will include CCI [redacted] CCI [redacted] CCI [redacted] to serve as a standard of care control). An overview of the study design is provided in Section 1.2, Figure 1.

**There are 2 investigational products** in ***Part A*** (see also Section 6.1, Table 7):

1. CV0601, a monovalent modified-nucleoside mRNA COVID-19 vaccine encoding CCI [redacted] spike protein.
2. CV0701, a bivalent modified-nucleoside mRNA COVID-19 vaccine encoding spike proteins: 1) CCI [redacted] (CV0801) and 2) CCI [redacted] (CV0601).

CCI . The mRNA is encapsulated in LNPs CCI which enhance mRNA uptake into the cells where the mRNA is translated into antigen. CCI . The bivalent vaccine CV0701 will be presented as 2 separate components in glass vials. These components will be mixed in a separate 10 mL vial prior to administration according to directions provided in the Pharmacy Manual.

**Comparator:** CCI

CCI

### *4.1.2. Overall design of Part B*

***Part B of the randomized and observer-blind Phase 2 study will evaluate the safety, reactogenicity and immunogenicity of CV0801 (a monovalent modified-nucleoside mRNA COVID-19 vaccine encoding CCI spike protein) under 3 different storage conditions in healthy adults who have previously received a complete primary vaccination series with or without booster dose(s). Participants will be randomized equally across 3 arms:***

- ***Condition 1: CV0801 CCI baseline-control***
- ***Condition 2: CV0801 CCI intermediate storage conditions***
- ***Condition 3: CV0801 CCI maximum storage conditions***

***Condition 1 clinical trial material will serve as the baseline-control from which safety, reactogenicity and immunogenicity of Condition 2 and 3 (intermediate and maximum storage conditions) materials will be compared.***

***An overview of the study design is provided in Section 1.2, Figure 2.***

Details on safety monitoring by the Independent Data Monitoring Committee (IDMC) and internal Data Review Committee (iDRC) are provided in Section 8.5 for both parts of the study.

This study will be conducted by a contract research organization (CRO; PPD, part of Thermo Fisher Scientific).

## *4.2.* Scientific rationale for study design

### 4.2.1. Scientific rationale for study design for Part A

Interim data from the CV0501 Phase 1 study informs the study design of Part A (CV0701 and CV0601 Phase 2 study). This is founded on the basis that a similar safety profile can be expected as these investigational vaccines CCI [redacted] These 2 vaccine candidates will be compared against CCI [redacted] which represents current standard of care, in a randomized, observer-blinded, and contemporaneously enrolled study. Part A of the Phase 2 study measures post-vaccination serum neutralization titers for its main immunologic endpoints. Post-vaccination neutralizing titers have been associated with COVID-19 vaccine efficacy in several analyses of CCI [redacted] studies leading to vaccine authorization or licensure [Feng, 2021; Fong, 2022; Fong, 2023; Gilbert, 2022]. Vaccine efficacy increased with the neutralizing titer in each of these analyses of mRNA vaccines. These associations within a clinical study setting are additionally supported by meta-analyses of vaccine effectiveness within large populations, mechanistic biologic studies of nonhuman primates and therapeutic intravenous administration of virus neutralizing monoclonal antibodies.

### *4.2.2. Scientific rationale for study design for Part B*

***mRNA vaccine stability is affected by product-specific characteristics (such as molecular weight, buffer, lipid nanoparticle [LNP] encapsulation, etc), manufacturing processes-specific characteristics such as the length of time the vaccine is in liquid form (either during manufacturing, fill and finish, or during preparation and handling of the vaccine at different temperatures), and storage conditions of the finished product.***

***The effect of these manufacturing and storage conditions on the final attributes of the vaccine is mainly derived from product and process knowledge and from clinical experience collected throughout all phases of product development.***

***Through this Part B of the Phase 2 study, the Companies (GSK and CureVac) aim to develop data on products stored at different conditions within a clinical trial setting. In doing so, this amendment will compare the safety, reactogenicity, and Day 29 immunogenicity of 2 specifications of booster dose investigational COVID-19 mRNA vaccines exposed to storage conditions.***

## 4.3. Justification for dose

The doses to be evaluated in this Phase 2 study are:

- CV0701 Bivalent CCI : CCI
- CV0701 Bivalent CCI : CCI
- CV0701 Bivalent CCI : CCI
- CV0601 Monovalent CCI : CCI
- ***CV0801 Monovalent CCI : CCI at 3 different storage conditions.***

The bivalent and monovalent doses selected in this study are based on interim safety and immunogenicity data from the CV0501 Phase 1 study.

The CV0501 Phase 1 is an open-label study enrolling healthy adults 18 years of age and older who have previously completed at least a 2-dose priming series of the original monovalent mRNA COVID-19 vaccines. Booster doses were allowed if the 6-month timeframe since vaccination was maintained. The 2-part study of 180 participants includes a Part A dose-escalation phase in which 5 sequential cohorts (n=30 per dose group) were enrolled to receive doses ranging from CCI to CCI. Participants aged 18 to 64 years formed the Younger Adults age-dose cohorts; the Older Adults age-dose cohorts comprised participants aged 65 or older. Part B is a prospectively designed dose-down portion of the study evaluating CCI and CCI dose levels (n=15 participants per dose) in an 18 to <65-year age group. CV0501 safety is assessed by evaluating solicited and unsolicited adverse events (AEs), medically attended AEs (MAAEs), serious AEs (SAEs), and AESIs. Immunogenicity is evaluated through SARS-CoV-2 neutralizing levels against CCI (strain matched to the variant encoded in CV0501) and CCI (strain for scientific comparative purposes), in addition to other planned assessments of the immune response including binding immunoglobulin G (IgG) and cell-mediated immunity.

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CCI Additionally, all Phase 2 doses will be compared to the CCI CCI This will enable comparisons to be made between monovalent and bivalent CCI containing vaccines contemporaneously, in a randomized design, within a single study population.

In Part B of the Phase 2 study, the CCI dose will provide exploratory data on any changes in reactogenicity, safety and immunogenicity due to reduced vaccine stabiltiy under different storage conditions, at doses levels consistent with Part A, which allow for comparative assessment.

### 4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit.

The end-of-study (EoS) is defined as the date of last participant last visit (LLV; Visit 4/Phone call 3, Day 181) or the date of the last testing released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. The EoS must be achieved no later than 8 months after LPLV. The EoS cannot be before LPLV.

## 5. STUDY POPULATION

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

### 5.1. Inclusion criteria

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

1. Is at least 18 years old and has achieved legal age according to local regulations in each participating country.
2. Must provide documented informed consent prior to any study procedures being performed.
3. Can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits), in the opinion of the investigator.
4. Is healthy or medically stable as determined by the investigator's judgment based on medical history, vital sign measurements, and physical examination findings. Participants with pre-existing stable disease, defined as disease not requiring

significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

5. Prior receipt of an mRNA COVID-19 vaccine. This may be from a completed primary vaccination series or booster dose(s) of an approved or authorized mRNA COVID-19 vaccine. The last vaccination must be an mRNA COVID-19 vaccination received at least 3 months prior to randomization.
6. If the participant is a woman of childbearing potential, the participant may be enrolled in the study, if she has:
   - practiced adequate contraception for 30 days prior to study intervention administration; and
   - has a negative pregnancy test result on the day of study intervention administration; and
   - has agreed to continue adequate contraception for 2 months after study intervention administration.

   Refer to Section 10.4.1 for definitions of woman of childbearing potential and adequate contraception.

   Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as current salpingectomy , hysterectomy, ovariectomy, or postmenopause. Refer to Section 10.4.1 for definitions of women of childbearing potential, menarche and menopause.

## 5.2. *Exclusion criteria*

Participants are excluded from the study if any of the following criteria apply:

1. Is pregnant or has a positive pregnancy test result at Visit 1.
2. Is breastfeeding or will (re)start breastfeeding from the study intervention administration to 3 months after study intervention administration.
3. Has any medical disease or psychiatric condition that, in the opinion of the investigator, precludes study participation because it would place the participant at an unacceptable risk of injury, would render them unable to meet the requirements of the protocol, or may interfere with successful completion of the study.
4. Has any history of an immunosuppressive or immunodeficient condition resulting from disease (e.g., HIV infection or congenital immunodeficiency).
5. Has used immunosuppressants or other immune-modifying drugs for 14 consecutive days or more within 3 months prior to the study intervention administration (for corticosteroids, this will mean prednisone ≥20 mg/day or equivalent). Non-systemic (e.g., inhaled, topical, or intra-articular) corticosteroids are allowed. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration.

6. Has an acute medical illness or acute febrile illness with oral temperature ≥38.0°C or ≥100.4°F within 72 hours prior to study intervention administration.
7. Has participated in another study involving any investigational product, vaccine, or device within 28 days before the study intervention administration and/or planned participation through EoS.
8. ***Has participated in Part A of this study.***
9. Has a history of hypersensitivity or severe allergic reaction including anaphylaxis, generalized urticaria, angioedema, and other significant reactions to any previous mRNA vaccine or any component of the study intervention(s).
10. Has received or plans to receive immunoglobulins or any blood or blood products within 3 months before study intervention administration through EoS.
11. Has a bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections.
12. Has a history of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures.
13. Has a history of myocarditis, pericarditis, 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 and persistent myocardial infection.
14. Has received a live vaccine 30 days before the study intervention administration or has a planned administration within 30 days after the study intervention administration.
15. Has received a non-replicating vaccine (e.g., inactivated and subunit influenza vaccine or pneumococcal conjugate vaccine) 8 days before the study intervention administration or has a planned administration within 14 days after the study intervention administration.
16. Has a history of SARS-CoV-2 infection within 3 months before study intervention administration.
17. Has had known close contact with anyone who had a confirmed SARS-CoV-2 infection within 2 weeks before study intervention administration.
18. Is an employee or family member of the investigator or study site staff.

## 5.3. Lifestyle considerations

Not applicable for this study.

## 5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study intervention/entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any SAE.

Participants who do not meet the criteria for study entry may be rescreened if the reason for exclusion may have changed. A new participant number will be assigned when a participant is rescreened. Previously assigned participant numbers are to be recorded in the participants' electronic case report form (eCRF).

## 5.5. Criteria for temporarily delaying administration of study intervention

If a protocol-related procedure needs to be conducted to confirm eligibility or if the participant is likely to fulfill the eligibility criteria after a period of delay, the study intervention administration may be postponed up to a maximum of 14 days until the result is obtained and/or eligibility can be confirmed. The participant can only be vaccinated once the investigator receives the results and/or confirms the eligibility criteria. The investigator should repeat the following screening evaluations (see also Table 1 and ***Table 2***) to confirm eligibility: inclusion/exclusion assessment, medical history, concomitant medication/vaccination recording, vital signs measurements, physical examination, and pregnancy test (for women of childbearing potential [WOCBP]).

# 6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

## 6.1. *Study interventions administered*

The study interventions administered in Part A include the CV0701 bivalent vaccine, CV0601 monovalent vaccine and comparator vaccine CCI [redacted] CCI [redacted]. The information on the study interventions is presented in Table 7.

***The study interventions administered in Part B include the CV0801 monovalent vaccine under 3 different storage conditions: baseline-control, intermediate and maximum storage condition. The information on the study interventions is presented in Table 8.***

**Table 7 Study intervention administered *for Part A***

| | Group A | Group B | Group C | Group D | Group E |
|---|---|---|---|---|---|
| **Study intervention name** | CV0701 Bivalent CCI CCI CCI | CV0701 Bivalent CCI CCI CCI | CV0701 Bivalent CCI CCI CCI | CV0601 Monovalent CCI CCI | CCI CCI CCI CCI |
| **Study intervention formulation** | Modified mRNA | Modified mRNA | Modified mRNA | Modified mRNA | Modified mRNA |
| **Presentation** | Glass vial as a sterile colloidal dispersion in a frozen liquid formulation* | Glass vial as a sterile colloidal dispersion in a frozen liquid formulation* | Glass vial as a sterile colloidal dispersion in a frozen liquid formulation* | Glass vial as a sterile colloidal dispersion in a frozen liquid formulation* | CCI CCI CCI CCI CCI CCI |
| **Route of administration** | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection |
| **Administration site location** | Deltoid | Deltoid | Deltoid | Deltoid | Deltoid |
| **No of doses** | 1 | 1 | 1 | 1 | 1 |
| **Unit dose strength(s)**** | CCI CCI CCI | CCI CCI CCI | CCI CCI CCI | CCI CCI | CCI CCI CCI |
| **Dose volume** | CCI | | | | |
| **Type (study intervention/ control)** | Study intervention | Study intervention | Study intervention | Study intervention | Comparator |

*The vaccines are vialed at a single concentration, and the final doses will be obtained with or without diluent prior to study intervention administration. CV0701 will be obtained by admixing the separate components (CV0601 and CV0801).

**This table references target clinical doses. The calculated mRNA dose level by dilution is referenced in the Pharmacy Manual.

***Table 8 Study intervention for Part B***

| | *Condition 1, baseline-control* | *Condition 2, intermediate storage conditions* | *Condition 3, maximum storage conditions* |
|---|---|---|---|
| *Study intervention name* | *CV0801 Monovalent* CCI [redacted] CCI *µg* | *CV0801 Monovalent* CCI [redacted] CCI *µg* | *CV0801 Monovalent* CCI [redacted] CCI *µg* |
| *Study intervention formulation* | *Modified mRNA* | *Modified mRNA* | *Modified mRNA* |
| *Presentation* | *Glass vial as a sterile colloidal dispersion in a frozen liquid formulation** | *Glass vial as a sterile colloidal dispersion in a frozen liquid formulation** | *Glass vial as a sterile colloidal dispersion in a frozen liquid formulation** |
| *Route of administration* | *Intramuscular injection* | *Intramuscular injection* | *Intramuscular injection* |
| *Administration site location* | *Deltoid* | *Deltoid* | *Deltoid* |
| *No of doses* | *1* | *1* | *1* |
| *Unit dose strength*** | CCI [redacted] CCI *µg* | CCI [redacted] CCI *µg* | CCI [redacted] CCI *µg* |
| *Dose volume* | CCI [redacted] | | |
| *Type (study intervention/ control)* | *Study intervention* | *Study intervention* | *Study intervention* |

***The vaccines are vialed at a single concentration, and the final doses will be obtained with diluent prior to study intervention administration.***
****This table references target clinical doses.***

Study participants must be observed closely for at least 30 minutes after the administration of the study intervention. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope or any other AEs following vaccination.

## 6.2. Preparation, handling, storage, and accountability

Refer to the Pharmacy Manual for instructions on how to prepare and dispense the study interventions. Appropriately qualified and experienced study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist), as allowed by local, state, and institutional guidance, should prepare and dispense the study interventions. A second staff member will verify the dispensing. The following activities must be performed:

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

- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or other specified location.

## 6.3. Assignment to study intervention

Participants will be randomly assigned (1:1:1:1:1 ***in Part A and 1:1:1 in Part B***) to the study groups using a central randomization system. The randomization will be based on permutation blocking scheme using country, previous known COVID-19 (yes, no), and age (< 65 years, ≥65 years) as stratification factors.

## 6.4. Blinding

The study will be conducted in an observer-blind manner, meaning that participants, the site, and sponsor personnel involved in the clinical evaluation of the participants will be blinded to treatment allocation. Other study personnel, such as the study pharmacist, may be aware of the treatment assignment. To maintain the observer-blind, the vaccines will be prepared and administered by unblinded qualified study personnel who will not participate in data collection, evaluation, review or entry of any study endpoint (i.e., safety or immunogenicity).

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization has been conducted accurately.

A participant may continue in the study if that participant's intervention assignment is unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

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 the investigators in accordance with local regulations and/or GSK policy.

***Blinding of laboratory testing***

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

***Emergency unblinding***

The central randomization system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion,

contact GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

If the investigator is unable to access the central randomization system, they can contact the IRT helpdesk based on the information provided in the Pharmacy Manual.

A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

## 6.5. Study intervention compliance

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

## 6.6. Dose modification

Not applicable.

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

No long-term evaluation study is planned.

## 6.8. Treatment of overdose

There is no specific treatment or monitoring plan recommended for a vaccine overdose.

The investigator should use medical judgment and consult the sponsor if a participant receives a greater vaccine dose than allowed per protocol.

## 6.9. Prior and concomitant therapy

Any concomitant medication/vaccination deemed necessary for the welfare of the participant during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication/vaccination are recorded fully in the eCRF. No concomitant medications will be provided by the sponsor or PPD.

Please refer to the exclusion criteria (Section 5.2) for time permitted between receiving the study intervention and a concomitant vaccination.

Use of all concomitant medications and vaccinations within 6 months prior to eligibility assessment to the end of the study will be recorded in the participant's eCRF.

All prior COVID-19 vaccines received (including those received more than 6 months before eligibility assessment) and all COVID-19 vaccines received during the study will be recorded.

The minimum requirement is that the drug name and the dates of administration are recorded. This will include all prescription drugs and vaccinations. In addition, any herbal products, vitamins, minerals, and over-the-counter medications taken within 2 weeks of study intervention administration should also be recorded in the participant's eCRF. Any changes in concomitant medications should be recorded in the participant's eCRF throughout the study.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of study intervention

As this is a single dose study, discontinuation from study intervention does not apply.

## 7.2. Participant discontinuation/withdrawal from the study

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

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

All data and samples collected up to and including the date of withdrawal or of last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

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

| Reasons | Additional items/Sub-reasons |
|---|---|
| AE | Unsolicited AE<br>Solicited AE<br>AESI<br>SAEs<br>Other |
| Lost to follow-up | Participant relocated<br>Participant was incarcerated<br>Other, specify<br>Unknown |
| Physician Decision | Specify |
| Withdrawal by Participant | Burden of procedure<br>Participant relocated<br>Pursue alternative treatment<br>COVID-19 pandemic<br>Other |
| Other | Specify |

Participants who are withdrawn from the study because of AEs must be clearly distinguished from participants who are withdrawn for other reasons. The investigator will follow up participants who are withdrawn from the study due to an AE until the event is resolved (see Section 10.3.6.6).

## 7.3. Lost to follow-up

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

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

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

# 8. *STUDY ASSESSMENTS AND PROCEDURES*

- Study procedures and their timing are summarized in the SoA (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes, provided these procedures have met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- Safety and laboratory results that could unblind the study will not be reported to the investigative sites or other blinded personnel until the study has been unblinded.

In ***Part A***, an overall volume of approximately 200 mL will be collected from each participant over the entire study period. Additional blood volume (~60 mL) may be required for the participants in the CCI

***In Part B, an overall volume of approximately 40 mL will be collected from each participant over the entire study period***.

Repeat or unscheduled samples may be taken for safety reasons or due to technical issues with the samples.

## 8.1. Administrative and general/baseline procedures

### 8.1.1. Demographics

Record demographic data such as age, 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 study participants, and to determine if the study participants are truly representative of the impacted population.

### 8.1.2. Medical/vaccination history

For establishment of participant's eligibility, mRNA COVID-19 vaccination history should be achieved based on locally accepted documentation of vaccination. Other medical/vaccination history should be obtained by interviewing the participant and/or review of the participant's medical records.

A record of any pre-existing conditions, signs, and/or symptoms present prior to the administration of the study intervention dose should be in the eCRF.

## 8.2. *Immunogenicity assessments*

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

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK, or a contracted partner, to use the samples for further research. The further research will be subject to prior institutional review board/independent ethics committee (IRB/IEC) 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.

Planned timepoints for all immunogenicity assessments are provided in the SoA (Table 1 ***and Table 2).*** Blood samples on Day 1 should be collected as last procedure following eligibility assessment prior to vaccination.

### 8.2.1. Biological samples

Blood samples for humoral immune response testing will be taken from all study participants. A subset of ***Part A*** participants (targeting 25% of the total enrollment ***in Part A***) will undergo additional blood sampling for CCI [redacted] CCI [redacted] to evaluate CCI [redacted]. Immunogenicity assessments will be performed at sponsor-designated laboratories as detailed in the Laboratory Manual.

A SARS-CoV-2 swab for reverse transcription polymerase chain reaction (RT-PCR) testing should be obtained on Day 1 to establish infection status at vaccination. In case of acute COVID-19 assessment, a SARS-CoV-2 swab for RT-PCR testing may also be collected at an unscheduled visit (see Section 8.4.4.2 for details).

Refer to Table 9 and SoA (Table 1 and ***Table 2***) for information on samples collected for different assessments.

**Table 9 Biological samples**

| Sample type | Quantity | Unit | Timepoint | Subset name |
|---|---|---|---|---|
| ***Part A*** | | | | |
| Blood for humoral immunogenicity | ~56 | mL | Days 1, 29, 91 and 181 | All participants |
| CCI [redacted] | | | | |
| Nasopharyngeal or mid-turbinate swab specimen | - | - | Day 1 and case-driven | Participants with any symptoms of COVID-19 |
| ***Part B*** | | | | |
| ***Blood for humoral immunogenicity*** | ***~20*** | ***mL*** | ***Days 1 and 29*** | ***All participants*** |
| ***Nasopharyngeal or mid-turbinate swab specimen*** | ***-*** | ***-*** | ***Day 1 and case-driven*** | ***Participants with any symptoms of COVID-19*** |

CCI [redacted]

Additional exploratory testing to characterize the immune response of the vaccine/vaccine components (e.g., SARS-CoV-2 CCI [redacted] assays, assays to measure cross-reactive antibodies against other coronaviruses) or to characterize the disease may be performed on study samples if deemed necessary for accurate interpretation of the data and/or should such test(s) become available in the GSK's laboratory or in a laboratory designated by GSK. These additional assays may not be represented in the objectives/endpoints of the study protocol.

### 8.2.2. Laboratory assays

Anti-spike neutralization activity in serum will be measured using pseudotyped virus neutralization assays with pseudotyped virus displaying spike proteins from SARS-CoV-2 CCI [redacted]. Neutralization titers to other SARS-CoV-2 variants may also be tested. Binding IgG antibody (Ab) levels against SARS-CoV-2 CCI [redacted], and/or SARS-CoV-2 spike antigens from other variants will be measured. Serology testing for SARS-CoV-2 anti-nucleocapsid antibody will be performed to assess for prior SARS-CoV-2 infections.

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

**Table 10 Laboratory assays**

| Test Classification | System | Component | Method | Laboratory* |
|---|---|---|---|---|
| | | ***Part A*** | | |
| **Serum neutralization titers** | Serum | SARS-CoV-2 serum neutralization | Pseudotyped virus neutralization assay | Nexelis, a Q² solutions company |
| **Humoral immunity** | Serum | SARS-CoV-2 binding IgG | Multiplex electro-chemiluminescence assay | PPD BioA Lab |
| CCI | Serum | SARS-CoV-2 N protein serology (Ab) | Electro-chemiluminescence immunoassay (ECL | PPD GCL |
| CCI | | | | Cevac or GSK |
| **Molecular biology** | Nasopharyngeal or mid-turbinate swab | SARS-CoV-2 | RT-PCR | PPD GCL |
| **Molecular biology** | Nasopharyngeal or mid-turbinate swab | SARS-CoV-2 lineage/spike seq | Sequencing (NGS) | PPD GCL |
| | | ***Part B*** | | |
| **Serum neutralization titers** | ***Serum*** | ***SARS-CoV-2 serum neutralization*** | ***Pseudotyped virus neutralization assay*** | ***Nexelis, a Q² solutions company*** |
| **N protein serology (qualitative diagnostic assay)** | ***Serum*** | ***SARS-CoV-2 N protein serology (Ab)*** | ***Electro-chemiluminescence immunoassay (ECL)*** | ***PPD GCL*** |
| **Molecular biology** | ***Nasopharyngeal or mid-turbinate swab*** | ***SARS-CoV-2*** | ***RT-PCR*** | ***PPD GCL*** |

Ab: antibody; CCI ; IgG: immunoglobulin G; NGS: next-generation sequencing; RT-PCR: reverse transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
*Refer to the list of clinical laboratories for details.

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

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

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

### 8.2.3. Immunological read-outs

**Table 11 Immunological read-outs**

| Blood sampling timepoint | | Subset name | No. participants | Component |
|---|---|---|---|---|
| Type of contact and timepoint | Sampling timepoint | | | |
| ***Part A*** | | | | |
| **Humoral immunity (on serum samples)** | | | | |
| Visit 1 (Day 1)<br>Visit 2 (Day 29)<br>Visit 3 (Day 91)<br>Visit 4 (Day 181) | Pre-vaccination<br>1 month post-dose<br>3 months post-dose<br>6 months post-dose | All participants | ~415 | SARS-CoV-2 serum neutralization |
| | | | | SARS-CoV-2 binding IgG |
| | | | | SARS-CoV-2 N protein serology (Ab) |
| CCI [redacted] | | | | |
| ***Part B*** | | | | |
| ***Humoral immunity (on serum samples)*** | | | | |
| ***Visit 1 (Day 1)***<br>***Visit 2 (Day 29)*** | ***Pre-vaccination***<br>***1 month post-dose*** | ***All participants*** | ***~249*** | ***SARS-CoV-2 serum neutralization*** |
| | | | | ***SARS-CoV-2 N protein serology (Ab)*** |
| CCI [redacted] | | | | |

## 8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1 ***and Table 2***).

### 8.3.1. Physical examination

A complete physical examination (including height and weight) will be performed on Day 1 prior to study intervention administration for each participant.

Physical examination at each study visit after the study intervention administration visit will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if it is deemed necessary by the investigator or designee.

### 8.3.2. Vital signs

Vital signs will be measured in a sitting position after at least 5 minutes of rest and will include temperature (oral temperature is preferred), pulse rate, respiration rate, and systolic and diastolic blood pressure.

Vital sign measurements should be collected before and after study intervention administration on Day 1 and at the unscheduled visit for participants with any symptoms of COVID-19, myocarditis or pericarditis.

Per standard clinical practice, vital sign measurements may be repeated per investigator's discretion.

### 8.3.3. Pregnancy testing

WOCBP must perform a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

## 8.4. AEs, SAEs, and other safety reporting

Safety will be assessed through the collection and evaluation of solicited AEs (Section 10.3.3), unsolicited AEs (Section 10.3.4), MAAEs (Section 10.3.6), SAEs (Section 10.3.6), and AESIs (Section 10.3.6). Solicited administration site AEs will include injection site pain, redness, swelling, and lymphadenopathy (localized axillary, cervical, or supraclavicular swelling or tenderness ipsilateral to the vaccination arm). Solicited systemic AEs will include fever, fatigue, headache, chills, myalgia, and arthralgia.

AESIs will include the following:

- Laboratory-confirmed moderate to severe case of COVID-19
- Potential immune-mediated disorders (pIMDs)
- Myocarditis and pericarditis
- Anaphylaxis or severe hypersensitivity within 24 hours after study intervention administration

All suspected cases of COVID-19, myocarditis, and pericarditis in study participants will be diagnosed and clinically evaluated, which may require unscheduled study site visits and additional SARS-CoV-2 laboratory testing.

See Section 10.3 for definitions relating to safety information.

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 all AEs (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

Safety will also be assessed by physical examinations and vital sign measurements (as detailed in Sections 8.3.1 and 8.3.2, respectively).

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

All solicited AEs will be collected for a 7-day follow-up period after study intervention administration (i.e., from Day 1 through Day 7).

All unsolicited AEs will be collected for a 28-day follow-up period after study intervention administration (i.e., from Day 1 through Day 28).

All SAEs, MAAEs and AESIs will be collected from the start of study intervention until study end.

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-investigational medicinal product [IMP]) will be recorded from the time a participant consents to participate in the study until study end.

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

**Table 12 Collection and reporting of safety information**

| | Pre-Dose* | Study vaccine dose Day 1 | Day 7 | Day 28 | Study conclusion (Day 181) |
|---|---|---|---|---|---|
| Solicited AEs | | ■ | ■ | | |
| Unsolicited AEs | | ■ | ■ | ■ | |
| AESIs/MAAEs/SAEs | | ■ | ■ | ■ | ■ |
| SAEs related to study participation or concurrent GSK medication/vaccine** | ■ | ■ | ■ | ■ | ■ |
| AEs/SAEs leading to withdrawal from the study | | ■ | ■ | ■ | ■ |
| Pregnancy | | ■ | ■ | ■ | ■ |

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

* i.e., consent obtained on Day 1 (prior to vaccination).

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

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 10.3.6.2/Table 12.

Investigators are not obligated to actively seek information on AEs or SAEs after the 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 non-leading verbal questioning or the electronic diary (eDiary) 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/AESI, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (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 10.3.6.6.

### 8.4.4. AESIs

The study will capture the following specific AESIs:

- pIMDs
- Any laboratory-confirmed moderate to severe case of COVID-19
- Myocarditis and pericarditis
- Anaphylaxis or severe hypersensitivity within 24 hours after study intervention administration

All suspected cases of COVID-19, myocarditis, and pericarditis in study participants will be diagnosed and clinically evaluated, which may require unscheduled study site visits and additional testing based on the investigator's judgment.

#### 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 13. Please refer to the Section 10.3.6.8 for reporting details.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (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 study intervention administration) or as an exacerbation of a pre-existing chronic condition (if it exacerbated following study intervention administration) in the eCRF.

**Table 13 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:<br>• Autoimmune / Immune-mediated myocarditis<br>• Autoimmune / Immune-mediated pericarditis<br>• Giant cell myocarditis |
| Idiopathic pulmonary fibrosis | Including but not limited to:<br>• Idiopathic interstitial pneumonia (frequently used related terms include “Interstitial lung disease”, “Pulmonary fibrosis”, “Immune-mediated pneumonitis”)<br>• Pleuroparenchymal fibroelastosis (PPFE) |
| Pulmonary alveolar proteinosis (PAP) | • Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis” |

| Medical Concept | Additional Notes |
|---|---|
| **Endocrine disorders** | |
| Addison's disease | |
| Autoimmune / Immune-mediated thyroiditis | Including but not limited to:<br>• Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)<br>• Atrophic thyroiditis<br>• Silent thyroiditis<br>• 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 |
| **Eye disorders** | |
| Ocular Autoimmune / Immune-mediated disorders | Including but not limited to:<br>• Acute macular neuroretinopathy (also known as acute macular outer retinopathy)<br>• Autoimmune / Immune-mediated retinopathy<br>• Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia<br>• Cogan's syndrome: an oculo-audiovestibular disease<br>• Ocular pemphigoid<br>• Ulcerative keratitis<br>• Vogt-Koyanagi-Harada disease |
| **Gastrointestinal disorders** | |
| Autoimmune / Immune-mediated pancreatitis | |
| Celiac disease | |
| Inflammatory Bowel disease | Including but not limited to:<br>• Crohn's disease<br>• Microscopic colitis<br>• Terminal ileitis<br>• Ulcerative colitis<br>• 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:<br>• Dermatomyositis<br>• Inclusion body myositis<br>• Immune-mediated necrotizing myopathy<br>• Polymyositis |
| Mixed connective tissue disorder | |
| Polymyalgia rheumatica (PMR) | |
| Psoriatic arthritis (PsA) | |

| Medical Concept | Additional Notes |
|---|---|
| Relapsing polychondritis | |
| Rheumatoid arthritis | Including but not limited to:<br>• Rheumatoid arthritis associated conditions<br>• Juvenile idiopathic arthritis<br>• Palindromic rheumatism<br>• Still's disease<br>• Felty's syndrome |
| Sjögren's syndrome | |
| Spondyloarthritis | Including but not limited to:<br>• Ankylosing spondylitis<br>• Juvenile spondyloarthritis<br>• Keratoderma blenorrhagica<br>• Psoriatic spondylitis<br>• Reactive Arthritis (Reiter's Syndrome)<br>• 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) |
| 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:<br>• Acute necrotizing myelitis<br>• Bickerstaff's brainstem encephalitis<br>• Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)<br>• Myelin oligodendrocyte glycoprotein antibody-associated disease<br>• Neuromyelitis optica (also known as Devic's disease)<br>• Noninfective encephalitis / encephalomyelitis / myelitis<br>• 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:<br>• Cranial nerve neuritis (e.g., Optic neuritis)<br>• Idiopathic nerve palsies/paresis (e.g., Bell's palsy)<br>• Melkersson-Rosenthal syndrome<br>• Multiple cranial nerve palsies/paresis |
| Multiple sclerosis (MS) | Includes the following:<br>• Clinically isolated syndrome (CIS)<br>• Malignant MS (the Marburg type of MS)<br>• Primary-progressive MS (PPMS)<br>• Radiologically isolated syndrome (RIS)<br>• Relapsing-remitting MS (RRMS)<br>• Secondary-progressive MS (SPMS)<br>• Uhthoff's phenomenon |
| Myasthenia gravis | • Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome |
| Narcolepsy | • Includes narcolepsy with or without presence of unambiguous cataplexy |

| Medical Concept | Additional Notes |
|---|---|
| Peripheral inflammatory demyelinating neuropathies and plexopathies | Including but not limited to:<br>• Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy)<br>• Antibody-mediated demyelinating neuropathy<br>• Chronic idiopathic axonal polyneuropathy (CIAP)<br>• Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)<br>• 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:<br>• IgA nephropathy<br>• IgM nephropathy<br>• C1q nephropathy<br>• Fibrillary glomerulonephritis<br>• Glomerulonephritis rapidly progressive<br>• Membranoproliferative glomerulonephritis<br>• Membranous glomerulonephritis<br>• Mesangioproliferative glomerulonephritis<br>• Tubulointerstitial nephritis and uveitis syndrome |
| **Skin and subcutaneous tissue disorders** | |
| Alopecia areata | |
| Autoimmune / immune-mediated blistering dermatoses | Including but not limited to:<br>• Bullous Dermatitis<br>• Bullous Pemphigoid<br>• Dermatitis herpetiformis<br>• Epidermolysis bullosa acquisita (EBA)<br>• Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease<br>• Pemphigus |
| Erythema multiforme | |
| Erythema nodosum | |
| Reactive granulomatous dermatitis | Including but not limited to<br>• Interstitial granulomatous dermatitis<br>• 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:<br>• Toxic Epidermal Necrolysis (TEN)<br>• SJS-TEN overlap |
| Sweet's syndrome | • Includes Acute febrile neutrophilic dermatosis |
| Vitiligo | |
| **Vasculitis** | |
| Large vessels vasculitis | Including but not limited to:<br>• Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)<br>• Giant cell arteritis (also called temporal arteritis)<br>• Takayasu's arteritis |

| Medical Concept | Additional Notes |
|---|---|
| Medium sized and/or small vessels vasculitis | Including but not limited to:<br>• Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)<br>• Behcet's syndrome<br>• Buerger's disease (thromboangiitis obliterans)<br>• Churg–Strauss syndrome (allergic granulomatous angiitis)<br>• Erythema induratum (also known as nodular vasculitis)<br>• Henoch-Schonlein purpura (also known as IgA vasculitis)<br>• Microscopic polyangiitis<br>• Necrotizing vasculitis<br>• Polyarteritis nodosa<br>• Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)<br>• 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)" |
| Immunoglobulin G4 related disease | |
| Langerhans' cell histiocytosis | |
| Multisystem inflammatory syndromes | Including but not limited to:<br>• Kawasaki's disease<br>• Multisystem inflammatory syndrome in adults (MIS-A)<br>• Multisystem inflammatory syndrome in children (MIS-C) |
| Overlap syndrome | |
| Raynaud's phenomenon | |
| Sarcoidosis | • Includes Loefgren syndrome |
| Susac's syndrome | |

#### 8.4.4.2. SARS-CoV-2 infection, COVID-19 assessment and definitions

Participants will be instructed to inform the investigator immediately in the event of a positive SARS-CoV-2 test or suspected SARS-CoV-2 infection. In the absence of a confirmed alternative diagnosis, symptoms of suspected SARS-CoV-2 infection are:

- acute onset of fever and cough

  OR

- acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia.

All participants with suspected COVID-19 may have an unscheduled visit, as per the investigator's discretion, where they will undergo the assessments outlined in the SoA (Table 1 and ***Table 2***):

- Medical history
- SARS-CoV-2 RT-PCR (swab)

- Physical examination including vital sign measurements
- Review of AEs
- Review of concomitant medication/vaccination

When feasible, next generation sequencing will be performed on RT-PCR samples to determine the Pango lineage and WHO variants of concern.

COVID-19 diagnosis and clinical evaluation may be performed by an external medical provider or the study site. Any available isolate genotyping results will also be requested.

Participants with confirmed COVID-19 may also have an unscheduled convalescent visit(s) following recovery as per the investigator's discretion. At this visit, participants may undergo the assessments listed in the SoA (Table 1 and ***Table 2***).

All laboratory-confirmed SARS-CoV-2 infections (regardless of symptoms or time from study intervention administration) should be documented as AEs, but only confirmed moderate to severe cases of COVID-19 should be reported as AESIs. Severity of COVID-19 should be assessed as below:

- Grade 1 (Mild): An AE that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Grade 2 (Moderate): An AE that is sufficiently discomforting to interfere with normal everyday activities.
- Grade 3 (Severe): An AE that prevents normal, everyday activities. In adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.

Separate from any clinical assessment of SARS-CoV-2 infection in the study, a SARS-CoV-2 RT-PCR swab will be performed pre-vaccination and 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 timepoints specified in the SoA (Table 1 and ***Table 2***). The results of these assessments do not affect participant enrollment.

When there is enough evidence to make the diagnoses of confirmed moderate or severe COVID-19 infection, the AE must be reported as an AESI. Symptoms, signs, or conditions which might (or might not) lead to confirmed moderate or severe COVID-19 infection, should be recorded and reported as AEs, but not as AESIs, until the final or definitive diagnosis has been made and alternative diagnoses eliminated or shown to be less likely.

#### 8.4.4.3. Myocarditis and pericarditis assessment and definitions

All participants will be educated on the symptoms of myocarditis and pericarditis and will receive guidance on contacting study personnel and seeking medical care if any of these symptoms occur. All suspected or confirmed cases of myocarditis or pericarditis will be diagnosed and clinically evaluated.

Participants reporting acute chest pain, shortness of breath, palpitations, or other symptoms of myocarditis or pericarditis within 6 weeks after study intervention administration must be evaluated by a cardiologist with evaluation and management following current practice guidelines (e.g., American Heart Association or local standard of care).

Suspected cases of myocarditis or pericarditis are defined as having at least 1 sign/symptom of myocarditis or pericarditis and diagnostic findings including but not limited to the following:

- ECG abnormality that a cardiologist judges consistent with probable or possible myocarditis or pericarditis, including the following:
  - Sustained atrial or ventricular arrhythmias
  - Second-degree Mobitz type II or worse atrioventricular block, new bundle branch block
  - Diffuse ST-segment elevation or PR-segment depression, compatible with pericarditis
- An abnormal high sensitivity troponin I value that is confirmed abnormal on repeat testing.

Confirmed cases of myocarditis/pericarditis are defined as follows:

- Participants diagnosed by a cardiologist as a confirmed case of myocarditis/pericarditis based on international cardiac guidelines.

Participants who have confirmed myocarditis or pericarditis will have safety follow-up until resolution of symptoms and/or of abnormal test findings.

Functional cardiac evaluation (e.g., stress test echocardiogram) to detect potential late onset of cardiac function impairment must be performed in the event myocarditis or pericarditis is confirmed.

Suspected cases of myocarditis and pericarditis will be assessed by unblinded committees (see Section 8.5).

Symptoms or signs which might (or might not) lead to one of the diagnoses of myocarditis or pericarditis should be recorded and reported as AEs, but not as AESIs, until there is enough evidence supporting the diagnosis of myocarditis or pericarditis and alternative diagnoses eliminated or shown to be less likely.

All confirmed and suspected cases of myocarditis or pericarditis will be reported by the investigator to the sponsor within 24 hours of becoming aware of these AEs.

### 8.4.5. Regulatory reporting requirements for SAEs, AESI and other events

- 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 10.3.6.2 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 10.3.6.7.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

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

| Type of event | Initial reports | | Follow-up of relevant information on a previous report | |
|---|---|---|---|---|
| | Timeframe | Documents | Timeframe | Documents |
| SAEs | 24 hours* ‡ | electronic AEs report | 24 hours* | electronic AEs report |
| Pregnancies | 24 hours* | paper pregnancy notification report | 24 hours * | paper pregnancy follow-up report |
| AESIs | 24 hours** ‡ | electronic AEs report | 24 hours* | electronic AEs report |

*Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.
‡ For each SAE/AESI, the investigator must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.

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

### 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 the participant is discharged from the study.
- 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, considering local requirements. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. See Table *14* for reporting timeframes.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

### 8.4.7. Contact information for reporting SAEs, AESIs, and pregnancies

**Table 15 Contact information for reporting SAEs, AESIs, and pregnancies**

| **Study contact for questions regarding SAEs, AESIs, and pregnancies** |
|---|
| Contact PPD pharmacovigilance |
| **Contacts for reporting SAEs, AESIs, and pregnancies** |
| Available 24/24 hours and 7/7 days |
| SAE hotline: +1-800-201-8725 |
| Fax: +1-888-488-9697 |

### 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/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back-up.

## 8.5. Committees structure

### 8.5.1. IDMC

An unblinded IDMC will meet to review all available safety data at scheduled timepoints. For the interim analysis, all available safety and immunogenicity data will be reviewed. At any time, the IDMC may provide a recommendation to the sponsor whether the study should be stopped, modified, or continue unchanged. The basis for any decision will be the review of all available immunogenicity and/or safety data. Ethical and regulatory authorities will be notified per local requirements in the event the study halts or terminates early. Additional details of the IDMC will be provided in a separate charter.

The IDMC will meet at the following timepoints:

- After 20% of participants have completed solicited reporting period (Day 7) ***(Part A only)***.
- Interim analysis, which will be based on Day 29 data from ***Part A*** participants.
- Every 3 months until the end of the study ***(Part A and Part B)***
- Ad hoc meetings, as needed, to review safety data.

The composition of the IDMC will include a biostatistician and physicians with relevant clinical experience to the conduct of this study. This will include cardiologist(s) to provide expert input into cardiac-related AEs such as myocarditis and pericarditis, as well as physicians with prior experience serving on committees with a similar scope.

### 8.5.2. iDRC

An unblinded iDRC will review safety, reactogenicity, and immunogenicity data from the ***Part A*** Day 29 interim analysis to make recommendations on dose selection for a future CCI study. ***In addition, the iDRC will perform a review of the Part B Day 29 interim analysis.*** This committee will be limited to select senior experts from the sponsor. Details of this will be documented in an iDRC charter.

### 8.5.3. Safety Review Team (SRT)

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

The SRT will remain blinded to study group allocation.

## 8.6. Pharmacokinetics

Not applicable.

## 8.7. Pharmacodynamics

Not applicable.

## 8.8. Genetics

Not applicable.

## 8.9. Biomarkers

Not applicable.

### 8.10. Immunogenicity assessments

Immunogenicity is described in Section 8.2

### 8.11. Health economics or medical resource utilization and health economics

Not applicable.

## 9. STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalized prior to the first participant first visit 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 key secondary endpoints. Statistical analysis will be performed using SAS software Version 9.4 or later. ***Part A and Part B will be analyzed independently, the considerations outlined in this section apply separately to each part.***

### 9.1. Statistical hypothesis

There is no hypothesis testing in this study; where statistical methods are applied, the emphasis will be on estimation with 95% confidence interval (CI). To provide preliminary evidence CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] (see Section 9.3.2).

### 9.2. Analysis sets

The primary analysis of unsolicited AEs, MAAEs, SAEs, and AESIs will be based on the Exposed Set (ES), defined as data from all exposed participants.

The primary analysis of solicited AEs will be based on the Diary Set, defined as data from all exposed participants for whom diary data are available.

The primary analysis of immunogenicity will be based on the Per Protocol Set, defined as data from participants from the ES who were eligible, complied with vaccination as per protocol (e.g., vaccine not expired, with appropriate temperature storage), and had a pre-dose and Day 29 anti-neutralizing titer against either the CCI [redacted] CCI [redacted]. Immunogenicity data at a post-vaccination visit will be censored in case of noncompliance for the blood sample visit. Likewise, immunogenicity data after the following intercurrent event will be censored: COVID-19, immunosuppressive or immunodeficient conditions, COVID-19 vaccination and prohibited medication/vaccination after study intervention.

For all analyses, the study group will be defined by the vaccine administered at Visit 1.

## 9.3. Statistical analyses

### 9.3.1. General considerations

***Analyses will be completed separately for part A and B, respectively.*** All descriptive analyses will be performed by vaccine group on data available, namely missing data will not be replaced. Subgroup analyses for safety and immunogenicity endpoints may be performed in selected groups and will be described in the SAP. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, standard deviation, median, and quartiles).

### 9.3.2. Primary endpoints analysis

The group GMT ratio associated 2-sided 95% CI and p-value for the null hypothesis that group GMT ratio is below 0.67 will be based on group contrast from an ANCOVA model on $log_{10}$-transformed anti-neutralizing titer. The model will include the vaccine group, country, previous known COVID-19 infection (yes, defined by self-reporting or positive N protein at pre-vaccination, no), age (< 65 years, ≥ 65 years), and $log_{10}$-transformed pre-dose titer as fixed effects. For this model, a titer below a quantifiable threshold will be assigned half the threshold while a titer above a quantifiable threshold will be assigned the threshold.

The primary safety endpoints as detailed in ***Table 5 for Part A and Table 6 for Part B*** will be analyzed as described in the SAP. For all reactogenicity and other safety endpoints, descriptive summary statistics will be provided for the Diary set and ES, respectively.

### 9.3.3. Secondary endpoints analyses

The secondary endpoints detailed in ***Table 5 for Part A*** will be analyzed as described in the SAP. Listings will be provided, and graphical presentations will be considered as needed. In addition to descriptive statistics for continuous variables, CIs and quartiles will also be provided for continuous immunogenicity variables. Seroresponse rate with 95% CI, GMT of specific Ab with corresponding 95% CI and GMI from baseline of specific Ab with corresponding 95% CI will also be provided by group. The GMT, the GMI, and their 95% CI in each group will be analyzed using an ANCOVA ***on $log_{10}$-transformed tier*** with vaccine group, country, previous known COVID-19 infection (yes defined by self-reporting or positive N protein at pre-vaccination, no), age (< 65 years, ≥ 65 years) and $log_{10}$-transformed pre-dose titer as fixed effects.

### 9.3.4. Tertiary endpoints analyses

The tertiary endpoints ***for Part A*** detailed in ***Table 5*** will be analyzed as described in the SAP. Graphical presentations will be considered as needed.

## 9.4. Interim analyses

For each part, an interim analysis will be performed based on safety and immunogenicity data (neutralization titers matched to the variant encoded on the study vaccines) for all participants up to Day 29. This interim analysis will be performed on the ES. To maintain the study blinding, the unblinded analysis will be available to the IDMC, iDRC core members and study statisticians in charge of the analysis. ***In addition, aggregate summaries will be used for regulatory interaction before LSLV. However, all efforts will be made to ensure that participants, investigators and monitoring staff will continue to remain blinded.***

Analyses will be performed as follows:

- Interim analysis: up to Day 29 safety and immunogenicity data (neutralization titers matched to the variant encoded on the candidate vaccines) for all participants ***(Part A and B separately).***
- Final analysis: up to Day 181 safety ***(Part A and Part B separately)*** and immunogenicity ***(Part A and Part B separately)*** data for all participants.

## *9.5. Sample size determination*

### *9.5.1. Part A*

***In Part A,*** approximately 415 participants will be enrolled and randomized in a 1:1:1:1:1 ratio to receive 1 of the 3 CV0701 formulations, CV0601, or the comparator vaccine (i.e., 83 participants will be enrolled in each of the 5 groups).

The ***Part A*** study will provide preliminary evidence of CCI [redacted]

### *9.5.2. Part B*

***In Part B, a total of 249 participants will be enrolled and randomized in a 1:1:1 ratio to receive an injection of 1 of the 3 vaccine storage conditions (83 participants in each of the 3 groups).***

***Part B study will provide preliminary evidence of*** CCI [redacted]

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

### 10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines,
  - Applicable ICH GCP guidelines,
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC,
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
  - Providing oversight of the conduct of the study at the site and adherence to requirements of Title 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### 10.1.2. Financial disclosure

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

### 10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the requirements of Title 21 Code of Federal Regulation Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical, signed copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

### 10.1.4. Recruitment strategy

The study is planned to be conducted at sites in multiple countries. The recruitment plan will be defined by each participating site.

The recruitment plan may be adapted based on the actual number of participants enrolled in each country. In case a site would fall behind in participant recruitment, a redistribution of the enrollment target per site in the participating countries may be made. This would allow the other participating sites to enroll additional participants to ensure full and timely enrollment of the overall targeted number of participants specified in this protocol.

The procedures for participants identification/recruitment must be approved by the IRB/IEC together with the material intended for participants identification/recruitment and participants use. Refer to the Study Procedures Manual for additional details.

### 10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.
- The participant must be informed that 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 contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

### 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, including a summary of study results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.

- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure that the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

### 10.1.7. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be predefined in the Study Management Plan to identify systematic issues that can impact participant rights, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final clinical study report/equivalent summary unless local regulations or institutional policies require a different 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., endpoint adjudication committee, expert reader), documents are stored by the external body for 25 years.

### 10.1.8. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF/eDiaries or entered in the eCRF/eDiaries that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgment or monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 10.1.9. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10 will be performed at GSK's laboratory or in a laboratory designated by GSK.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

# 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.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. |

| Events Meeting the AE Definition |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.<br>• 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.<br>• Significant failure of an expected pharmacologic or biological action.<br>• Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen). |
| Events NOT Meeting the AE Definition |
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.<br>• 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. Other situations:

- Possible Hy's Law case: alanine transaminase ≥ 3x upper limit of normal (ULN) AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or international normalized ratio >1.5 must be reported as an 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 AEs

| Definition of Solicited AEs |
|---|
| • Solicited AEs are predefined administration site and systemic events for which the participant is specifically questioned and which are noted by the participant in their eDiary up to 6 days after study intervention administration, i.e., from Day 1 through Day 7. |

Solicited administration site AEs will include pain, redness, and swelling at the administration site and lymphadenopathy (localized axillary, cervical, or supraclavicular swelling or tenderness ipsilateral to the vaccination arm).

Solicited systemic AEs will include fever, fatigue, headache, chills, myalgia, and arthralgia. Note: Participants will be instructed to measure and record the temperature in the evening. Oral temperature measurement is preferred. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in their eDiary.

### 10.3.4. Unsolicited AEs

| 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 have 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 MAAE(s), as well as any events that, though not medically attended, are of participants' concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended or perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.

### 10.3.5. Definition of MAAE

| **MAAE Definition** |
|---|
| • An MAAE is defined as an AE that results in a visit to a medical professional (e.g., televisit, physician's office visit, urgent care visit, emergency room visit, or hospitalization). |

### 10.3.6. Recording, assessment, and follow-up of AEs, SAEs, MAAEs, AESIs, and pregnancies

#### 10.3.6.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

***Recording of solicited AEs***

An eDiary will be used in this study to capture solicited administration site and 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.

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 them to be reported directly to the site staff and submitted (e.g., via the eCRF).

Any unreturned eDiary devices will be sought from the participant through telephone call(s) or any other convenient procedure.

***Recording of MAAEs***

For each solicited and unsolicited AE the participant experiences, the participant will be asked if they received medical attention (defined as an 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).

Medical attention received for SAEs/AESIs will have to be reported using the normal AE reporting process in the eCRF.

#### 10.3.6.2. Time period for collecting and recording AEs, SAEs, MAAEs, AESIs and pregnancies

All solicited events that occur during the 7-day follow-up period after study intervention administration (Day 1 to Day 7) must be recorded into the eDiary, irrespective of intensity. An automatic reminder to complete the eDiary will be sent to the participants during this timeframe. All other AEs occurring within this timeframe should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

All unsolicited AEs that occur during the 28-day follow-up period after study intervention administration (Day 1 to Day 28) must be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

The time period for collecting and recording SAEs, MAAEs and AESIs will begin at the first receipt of study interventions and will end approximately 6 months after the last administration of the study interventions (at study end). The SAEs related to study participation or to a concurrent GSK medication/vaccine will be collected from the time consent is obtained until the participant is discharged from the study.

All AEs/SAEs leading to withdrawal from the study and pregnancies will be collected and recorded from the time of the first receipt of study intervention until the participant is discharged from the study (refer to Section 10.3.6.6 for details on follow-up of pregnancies). SAEs related to study participation or to a concurrent GSK medication/vaccine will be collected from the time informed consent is obtained until the

participant is discharged from the study. However, if the investigator learns of any SAE related to study participation after a participant has been discharged from the study, the investigator must promptly notify the sponsor.

#### 10.3.6.3. Assessment of intensity

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

**Table 16 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 | <2.5 cm |
| | 1 | 2.5 – 5 cm |
| | 2 | 5.1 – 10 cm |
| | 3 | >10 cm |
| Swelling at administration site | 0 | <2.5 cm |
| | 1 | 2.5 – 5 cm |
| | 2 | 5.1 – 10 cm |
| | 3 | >10 cm |
| 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 |
| Temperature** | 0 | <38.0°C or <100.4°F |
| | 1 | 38.0 – 38.4°C or 100.4 – 101.1°F |
| | 2 | 38.5 – 38.9°C or 101.2 – 102.0°F |
| | 3 | >38.9°C or >102.0°F |
| Headache | 0 | Normal |
| | 1 | Mild: Headache that is easily tolerated |
| | 2 | Moderate: Headache that interferes with normal activity |
| | 3 | Severe: Headache that prevents normal activity |
| Fatigue | 0 | Normal |
| | 1 | Mild: Fatigue that is easily tolerated |
| | 2 | Moderate: Fatigue that interferes with normal activity |
| | 3 | Severe: Fatigue that prevents normal activity |
| Myalgia | 0 | Normal |
| | 1 | Mild: No interference with daily activity |
| | 2 | Moderate: Interferes with daily activity |
| | 3 | Severe: Prevents daily activity |
| Arthralgia | 0 | Normal |
| | 1 | Mild: No interference with daily activity |
| | 2 | Moderate: Interferes with daily activity |
| | 3 | Severe: Prevents daily activity |

| Event | Intensity grade | Parameter |
|---|---|---|
| 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 |

* Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the vaccination arm.
** Refer to Section 10.3.3 for the preferred location for temperature measurement.

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

- Mild:
  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.

#### 10.3.6.4. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to PPD pharmacovigilance. 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 PPD pharmacovigilance.
- 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.

#### 10.3.6.5. 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)

#### 10.3.6.6. 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.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to PPD pharmacovigilance within 24 hours of receipt of the information.

After the initial AE/SAE/AESI/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts.

All SAEs, and nonserious AESIs (as defined in the Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Other nonserious AEs must be followed until the end of the study or until the participant is lost to follow-up.

***Follow-up during the study***

All AEs/SAEs/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 study end.

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, considering local requirements. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to PPD pharmacovigilance using the paper pregnancy follow-up 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 and should follow local requirements.

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 post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention to PPD pharmacovigilance as described in the Section 10.3.6.8.

#### 10.3.6.7. 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).

#### 10.3.6.8. Reporting of SAEs, AESIs and pregnancies

Reporting SAEs to PPD pharmacovigilance via an electronic data collection tool as follows:

- The primary mechanism for reporting an SAE 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 medical monitor by telephone.
- If the site during the course of the study or after the study ends becomes aware of any serious or nonserious AEs, pregnancy exposure, related to any GSK non-IMP, they will report these events to PPD pharmacovigilance or to the concerned

competent authority via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports.

- Contacts for SAE reporting can be found in Section 8.4.7.

Reporting SAEs to PPD pharmacovigilance via paper data collection tool as follows:

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- 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.

### 10.3.7. Study and site start and closure

**Start of study and first act of recruitment**

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

**Study/site termination**

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

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

## 10.4. Appendix 4: Contraceptive and barrier guidance

### 10.4.1. Definitions

#### 10.4.1.1. Women of childbearing potential

Women from the time of menarche until becoming postmenopausal unless permanently sterile (see below) are considered WOCBP (fertile).

#### 10.4.1.2. Women of non-childbearing potential

Women in the following categories are considered women of non-childbearing potential:

1. Permanently sterile due to one of the following procedures:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

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

2. Postmenopausal female

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

   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.4.2. Contraception guidance

- WOCBP 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 17).

**Table 17 Highly effective contraceptive methods**

| |
|---|
| Highly Effective Contraceptive Methods That Are User Dependent*<br>*Failure rate of <1% per year when used consistently and correctly* |
| Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Intravaginal<br>• Transdermal |
| Progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Injectable<br>• Oral |
| Highly Effective Methods That Are User Independent |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Intrauterine device<br>• Intrauterine hormone-releasing system<br>• Bilateral tubal occlusion/ligation |
| Vasectomized partner<br>*(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.<br>*(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<br>(*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.)* |

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

## 10.5. *Appendix 5: Protocol amendment history*

***Not Applicable***

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