Protocol Amendment 2

Study ID: 217741

Official Title of Study: A Phase 1, Open-label, Safety, Reactogenicity, and Immunogenicity Trial of the CV2CoV mRNA Vaccine Against SARS-CoV-2 in Seropositive Adult Participants

NCT number: NCT05260437

Date of Document: 14-Jun-2022

CLINICAL STUDY PROTOCOL

A Phase 1, Open-label, Safety, Reactogenicity, and Immunogenicity Trial of the CV2CoV mRNA Vaccine Against SARS-CoV-2 in Seropositive Adult Participants

PROTOCOL 217741 (CV2 SARS-COV2-002 BST)

Sponsor:	GlaxoSmithKline Biologicals SA Rue de l'Institut 89, 1330 Rixensart, Belgium
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Protocol Number:	217741
Abbreviated Title:	CV2 SARS-COV2-002 BST
Amendment Number:	Amendment 2
Date of Amendment 2	13 Jun 2022
Date of Amendment 1:	20 Apr 2022
Date of Original Protocol:	11 Feb 2022
Compound Name:	CV2CoV mRNA vaccine
Study Phase:	1
IND Number:	27859
EudraCT Number	2021-003093-31

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title:	A Phase 1, Open-label, Safety, Reactogenicity, and Immunogenicity Trial of the CV2CoV mRNA Vaccine Against SARS-CoV-2 in Seropositive Adult Participants
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Protocol Date and Version:	13 Jun 2022; Amendment 2
IND Number:	27859
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Protocol accepted and approved by:

Clinical Epidemiology Project Lead

Roshan Ramanathan, MD, MPH

GSK Rockville Center for Vaccines Research
14200 Shady Grove Road
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PPD

14 Jun 2022
Date

Declaration of Investigator

I have read and understood all sections of the protocol titled "A Phase 1, Open-label, Safety, Reactogenicity, and Immunogenicity Trial of the CV2CoV mRNA Vaccine Against SARS-CoV-2 in Seropositive Adult Participants" and the accompanying IB.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 2 dated 13 Jun 2022, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with GSK Biologicals SA or PPD or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to participants. I agree to administer study vaccine only to participants under my personal supervision or the supervision of a subinvestigator.

I will not supply the study vaccine to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from GSK Biologicals SA.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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List of Abbreviations

Abbreviation	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease caused by SARS-CoV-2
CV2CoV	SARS-CoV-2 second-generation vaccine (monovalent; targets wild type Wuhan strain [D614])
CVnCoV	SARS-CoV-2 first-generation vaccine (monovalent; targets wild type Wuhan strain [D614])
D	day
EDC	electronic data capture
eCRF	electronic case report form
eDiary	electronic diary
EOS	end of study
ET	early termination
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GMI	geometric mean increase
GMT	geometric mean titer
GSK	GlaxoSmithKline Biologicals SA
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator’s brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	intracellular cytokine staining assay

Abbreviation	Definition
IEC	independent ethics committee
IgG	immunoglobulin G
IND	investigational new drug
IM	intramuscular(ly)
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NA	not applicable
NIH	National Institutes of Health
N protein	nucleocapsid protein
PBMC	peripheral blood mononuclear cell
pIMD	potential immune-mediated diseases
PP	per protocol
SAP	statistical analysis plan
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
S protein	spike protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOE	schedule of events
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
Th	T helper
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential
WT	wild type

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	13 Jun 2022
Amendment 1	20 Apr 2022
Original Protocol	11 Feb 2022

Amendment 2, 13 Jun 2022: Current Amendment

Rationale for Amendment 2:

The main purposes of Amendment 2 are to make use of early trial experiences to further enhance study management at study sites, the scientific integrity of results, and further align the trial parameters with best medical practices and previous practices in similar trials.

The summary of changes table provided here describes the important changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. The synopsis of Amendment 2 has been modified, as needed, to correspond to changes in the body of the protocol. Minor editorial, grammatical, and formatting corrections are not included in this summary table.

Throughout the document, the protocol date and version were updated to reflect Amendment 2 and the title page was updated to reflect the protocol history.

Summary of Important Changes from Amendment 1 to Amendment 2:

Section Number and Name	Description of Change	Brief Rationale
Section 3.1 (Study Design)	Reduced the target number for total enrollment, from 210 to 180 participants, with a total of 30 participants in each dose group and a minimum of 10 and maximum of 20 participants in each age group within a dose group	To specify minimum target requirements for enrollment of older adults enrolled in the ongoing study
Section 3.1 (Study Design) Section 6.6 (SARS--CoV-2 and COVID-19 Disease Assessment and Definitions) Section 13.1 (Appendix 1: Schedule of Events)	Increased the length of the screening period from 7 to 14 days; SARS-CoV-2 RT-PCR sampling and testing will still occur within 7 days before Day 1	To allow investigators more time to assess eligibility of participants in the ongoing study

Section Number and Name	Description of Change	Brief Rationale
Section 3.2 (Rationale for Study Design) Section 6 (Study Assessments and Procedures) Section 13.1 (Appendix 1: Schedule of Events)	Clarified the use of televisits during the study	To enhance study management at study sites
Section 4.1.1 (Inclusion Criteria)	Changed inclusion criterion 3 to narrow enrollment to participants who received only Comirnaty® or Spkevax® vaccines, while opening enrollment to participants who had received booster vaccination at least 6 months prior to Screening	To permit enrollment of participants who have received booster vaccines per current standard of care
Section 4.1.1 (Inclusion Criteria)	Changed inclusion criterion 6 to permit inclusion of participants with BMI up to 34.9 kg/m^2	To clarify the eligibility criterion for persons in this BMI range who are not expected to be at increased risk due to study participation
Section 4.1.2 (Exclusion Criteria)	Deleted exclusion criterion 7 and moved it to exclusion criterion 24, removing distant smoking history from the exclusion criterion	To clarify the eligibility criterion for distant smokers who are not expected to be at increased risk due to study participation
Section 4.1.2 (Exclusion Criteria)	Edited exclusion criterion 24b to reflect a higher systolic blood pressure threshold for uncontrolled hypertension (150 mmHg) for participants > 60 years old	Clarification provided, since individuals with well controlled essential hypertension may be eligible for enrollment
Section 4.1.2 (Exclusion Criteria)	Added a new exclusion criterion 25, to exclude participants with a history of documented SARS-CoV-2 infection or COVID-19 within 6 months before Screening	To minimize the risk that a SARS-CoV-2 infection within the 6 months before Screening will confound the immunogenicity evaluation of study vaccine and to enhance the scientific integrity of results
Section 4.1.3 (Screen Failures)	Added a definition of screen failures and procedures both for documenting screen failures and for rescreening	To clarify that rescreening is permitted and what documentation and procedures are required

Section Number and Name	Description of Change	Brief Rationale
Section 5.9 (Study Holding Rules)	Clarified the application of the Bayesian logistic regression model	To clarify how the Bayesian logistic regression model is intended to be used
Section 6.1.2 (Clinical Safety Laboratory Assessments)	Added that SARS-CoV-2 RT-PCR testing may be repeated once for enrollment requirements	To enhance study management at study sites
Section 6.1.4 (Vital Signs)	Clarified that blood pressure measured at Screening for eligibility may be based on an average of up to 3 blood pressure measurements	Individual blood pressure measurements may be insufficient to provide a comprehensive hypertension assessment based on the dynamic nature of blood pressure fluctuation.
Section 13.2 (Appendix 2: Contraceptive Guidance and Pregnancy Information)	Added tubal ligation to the list of acceptable forms of primary contraception	To provide clarity to Investigators on acceptable forms of primary contraception and to enhance study management at study sites
Section 13.3 (Appendix 3: Bayesian Logistic Regression Model)	Clarified the use and interpretation of the Bayesian logistic regression model by the SRT	To clarify that the Bayesian logistic regression model is used by the SRT to evaluate Grade 3 solicited events and help make recommendations on dose expansion and escalation. The model is not used to determine when study hold rule 2a is triggered.
Section 13.5 (Appendix 5: Tables for Laboratory Abnormalities)	Added an instruction to investigators to provide institutional normal reference ranges for local laboratories	To enhance study management at study sites and enhance the scientific integrity of results

Protocol Synopsis

Protocol Number: 217741 (CV2 SARS-COV2-002 BST)

Title: A Phase 1, Open-label, Safety, Reactogenicity, and Immunogenicity Trial of the CV2CoV mRNA Vaccine Against SARS-CoV-2 in Seropositive Adult Participants

Short Title: Phase 1 Safety, Reactogenicity, and Immunogenicity Trial of CV2CoV mRNA Vaccine Against SARS-CoV-2 in Seropositive Adult Participants

Sponsor: GlaxoSmithKline Biologicals SA, Rue de l'Institut 89, 1330 Rixensart, Belgium

Study Phase: 1

Indication: Prevention of COVID-19 disease caused by SARS-CoV-2

Rationale: Due to the ongoing COVID-19 pandemic and the need for vaccines to provide protection against SARS-CoV-2 and variants of concern, GSK and CureVac are collaborating to develop the CV2CoV mRNA second-generation vaccine based on CureVac's mRNA vaccine platform. The second-generation vaccine is based on a modified mRNA construct from the first-generation CVnCoV vaccine. This is a Phase 1 first-time-in-human study designed to evaluate the safety, reactogenicity, and immunogenicity of the GSK-CureVac second-generation CV2CoV mRNA vaccine in a booster vaccination setting. The proposed study will support development of the platform, guide dose selection and support decisions as to whether the candidate vaccine should be further evaluated in advanced phase clinical trials.

Objectives and Endpoints:

Objectives	Endpoints
Primary – Safety	
To evaluate the safety and reactogenicity of CV2CoV at each dose level in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• Percentage of participants with MAAEs, SAEs, and AESIs from study vaccination through the end of the study (approximately 180 days after the study vaccine administration), each summarized separately • Percentage of participants with each solicited local and systemic AE within the 7-day postvaccination period (Days 1 to 7) • Percentage of participants with unsolicited AEs up to 28 days after study vaccination, including clinically relevant abnormal laboratory findings
Secondary – Immunogenicity	
To explore the dose response and effect of CV2CoV at each dose level on neutralizing Ab titers against pseudovirus bearing spike protein from SARS-CoV-2 WT in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• GMTs of neutralizing Ab titers against pseudovirus bearing spike protein from SARS-CoV-2 WT at each collection time point (Days 1, 8, 15, 29, 85, and 180) • Percentage of participants with seroresponse (≥4-fold rise from baseline) at Day 29 after the booster dose • GMI from baseline of neutralizing Ab titers against pseudovirus bearing spike protein from SARS-CoV-2 WT at each collection time point (Days 8, 15, 29, 85, and 180)
To describe serum-binding Ab (IgG) levels specific for vaccine antigens in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• GMTs of binding IgG against SARS-CoV-2 S protein and RBD at each collection time point (Days 8, 15, 29, 85, and 180) • GMI from baseline of binding IgG against SARS-CoV-2 S protein and RBD at each collection time point (Days 8, 15, 29, 85, and 180)

Note: Tertiary objectives and endpoints are included in the main protocol.

Diagnosis and Main Criteria for Inclusion and Exclusion: The study will enroll healthy adults (≥18 to <65 years of age for the younger adult group and ≥65 years of age for the older adult group) who have received at least 2 doses of Pfizer-BioNTech (Comirnaty®) or Moderna (Spikevax®) mRNA COVID-19 vaccine (with the last dose of vaccine received at least 6 months prior to Screening and has provided documentation of receiving the vaccination series) and is negative for SARS-CoV-2 infection (by RT-PCR test) at Screening. History of documented SARS-CoV-2 infection or COVID-19 within 6 months before Screening, previous participation in an investigational vaccine study with investigational vaccine administered within 6 months of study vaccination or close contact with anyone who had a confirmed SARS-CoV-2 infection within 14 days before study vaccination will exclude individuals from study participation.

Study Design: This Phase 1 study will evaluate the safety, reactogenicity, and immunogenicity of the CV2CoV vaccine in SARS-CoV-2 seropositive healthy adult participants. The study will be conducted in 5 sequential cohorts with dose escalation from 2 µg to 20 µg. A total of up to approximately 180 healthy adult participants will be enrolled, 30 per dose group. The 30 participants will be distributed between the younger (≥18 to <65 years old) and older (≥65 years old) age groups, with a minimum of 10 and a maximum of 20 participants in each age group. There will be 3 sentinel participants in each age group within each dose group.

The study will be open-label. Participants in all cohorts will be screened for eligibility up to 14 days before enrollment. On Day 1, participants will receive study vaccine according to their cohort (dose group) and age group, and study visits will proceed according to the SOE. Participants will be sequentially enrolled to the dose level assigned to their cohort.

Three sentinel participants in the younger age group (Cohort 1) will be enrolled before opening enrollment in the older age group (Cohort 1). Study vaccine administration must be separated by at least 20 hours between sentinel participants in all cohorts and all dose groups. Sentinel participants will remain on site for approximately 4 hours after study vaccination and the remainder of participants in each group will remain on site for approximately 60 minutes after study vaccination for safety monitoring. A safety follow-up telephone call to each sentinel participant in each dose group will be performed on Day 2 (at least 20 hours postvaccination). Vaccination of the next sentinel participant will proceed, provided the safety was acceptable for the prior sentinel(s) per investigator’s assessment.

Escalation to the next higher dose cohorts will be based on the SRT review of safety data from the same age group. Enrollment into Cohorts 2 and 3 (8 and 12 µg, respectively) will begin after the SRT has reviewed Days 1 to 8 safety data (including Day 8 laboratory data) from 3 sentinel participants from the previous dose cohort. Enrollment into Cohorts 4, and 5 (16 µg, and 20 µg, respectively), will begin after the SRT has reviewed Days 1 to 8 safety data from all participants in the previous dose cohorts.

Study Duration: The screening period will be up to 14 days, study vaccine administration will occur on Day 1, and participants will have up to approximately 180 days (6 months) of follow-up after study vaccine administration. Study assessments will be performed in an outpatient setting at qualified study sites.

Safety Assessments: Safety will be assessed through the collection and evaluation of solicited and unsolicited AEs, MAAEs, SAEs, and AESIs. Safety will also be assessed based on physical examinations, vital sign measurements, and clinical laboratory assessments.

Immunogenicity Assessments: Blood samples will be collected to evaluate vaccine-induced neutralizing and binding IgG Ab levels and cell-mediated immunity. Neutralizing Ab levels against pseudovirus bearing spike protein from SARS-CoV-2 WT and potentially pseudovirus bearing spike protein from other variants will be measured. Binding Ab IgG levels against SARS-CoV-2 S protein, RBD, N protein (from WT), and SARS-CoV-2 spike (from other variants) will be measured. Antispike (from WT and potentially other variants) T-cell responses will be explored.

Investigational Product, Dosage, and Route of Administration: Study vaccine will be administered on Day 1 as a single IM injection of 0.3 mL in the deltoid area, preferably in the nondominant arm.

The following IP will be used in the study:

Description	Investigational Product CV2CoV[a]
CCI [redacted]	CCI [redacted]
CCI [redacted]	WT CCI [redacted]
CCI [redacted]	CCI [redacted]

a. Product reference: CV07050201.

b. CCI [redacted]

Sample Size: Approximately 180 participants will be enrolled in the study, apportioned among cohorts, dose groups, and age groups according to the table below.

Cohort	Dose Group	Dose Level	Younger Adults ≥18 to <65 Years of Age	Older Adults ≥65 Years of Age	Total Dose Group Sample Size
1	1a	2 µg	10 ≤ n ≤ 20	10 ≤ n ≤ 20	30
	1b	4 µg	10 ≤ n ≤ 20	10 ≤ n ≤ 20	30
2	2	8 µg	10 ≤ n ≤ 20	10 ≤ n ≤ 20	30
3	3	12 µg	10 ≤ n ≤ 20	10 ≤ n ≤ 20	30
4	4	16 µg	10 ≤ n ≤ 20	10 ≤ n ≤ 20	30
5	5	20 µg	10 ≤ n ≤ 20	10 ≤ n ≤ 20	30

Statistical Methods: No formal significance testing will be performed. Analysis details, including any subgroup analysis, will be provided in the SAP.

For all safety endpoints, descriptive summary statistics will be provided for the Safety Set. Safety data listings will be provided, and graphical presentations will be considered as needed. In addition to the planned summary of SAEs throughout the study, any SAEs that are reported within 28 days of study vaccine administration will also be summarized.

For the immunogenicity endpoints, the GMTs of specific Ab with corresponding 95% CIs) at each time point and percentage of participants with seroresponse (≥4-fold rise from baseline) at Day 29 after the booster dose, and GMI from baseline of specific Ab with corresponding 95% CIs at each postbaseline time point over prevaccination baseline will be provided by dose group. The GMT, the GMI, and their 95% CI in all cohorts will be analyzed using an ANCOVA with treatment and age group as fixed factors and prevaccination baseline value as a covariable.

Version and Date of Protocol: Amendment 2; 13 Jun 2022

1 Introduction

1.1 Background Information

The COVID-19 pandemic caused by SARS-CoV-2 virus was declared by the WHO on 11 March 2020 (WHO 2020). As of 11 November 2021, more than 250 million cases have been reported worldwide, leading to more than 5.0 million deaths (WHO 2021). To date, there are several vaccines available, licensed, under emergency use authorizations or conditional approvals using different technologies. All available vaccines utilize antigens from the ancestral Wuhan strain (D614; wild type, hereafter referred to as "WT").

Recent scientific data highlight the potential for SARS-CoV-2 variants to escape from neutralizing humoral immunity and emphasize the need to develop broadly protective interventions, such as reformulation of existing SARS-CoV-2 vaccines to include diverse spike sequences. The development of new vaccines capable of eliciting broad neutralizing Ab responses is necessary.

CureVac developed a first-generation mRNA vaccine (CVnCoV) using WT, for which vaccine safety and efficacy are being evaluated (NCT04652102). Results from the Phase 2b/3 trial of CVnCoV showed a vaccine efficacy of 48% against COVID-19 of any severity across all age groups and 15 different virus strains; the vaccine safety profile was acceptable. In participants 18 to 60 years of age, significant vaccine efficacy was demonstrated, which included 53% efficacy against disease of any severity, and 77% efficacy against moderate and severe disease. The virus was sequenced in 204 cases to identify the variant causing the infection. Approximately 86% of these cases were caused by variants of concern (~51%) and variants of interest (~35%). Approximately 3% of cases were attributable to the ancestral SARS-CoV-2 virus while the remaining 11% were caused by less-explored strains; thus, further demonstrating the need for protection against emerging SARS-CoV-2 variants (Kremsner 2021).

To continue addressing an unmet public health need for products that provide protection against COVID-19 disease, GSK and CureVac are collaborating to develop CV2CoV mRNA second-generation vaccine based on CureVac's mRNA vaccine platform. The CV2CoV vaccine is based on a new mRNA backbone that features targeted optimizations designed to improve intracellular mRNA stability and translation for increased and extended protein expression. These optimizations potentially allow for strong immune responses at low doses,

which are intended to support the development of multivalent vaccines to target rapidly spreading COVID-19 variants (CureVac 2021).

Nonclinical data have shown promising results that indicate the second-generation mRNA vaccines have enhanced immunogenicity compared with the SARS-CoV-2 first-generation CVnCoV mRNA vaccine. Preclinical data in rats immunized with CV2CoV in the dose range of [redacted] demonstrated fast onset of strong immune responses after the first dose. In addition, the serum of vaccinated animals showed significant cross-neutralization against variants first discovered in Denmark (B.1.1.298), the United Kingdom (B.1.1.7), and South Africa (B.1.351) (CureVac 2021; Roth et al 2021). Refer to the IB for additional nonclinical information.

The CV2CoV vaccine will target SARS-CoV-2 WT. This second-generation vaccine will be intended for use as a booster dose in individuals who are SARS-CoV-2 seropositive due to prior COVID-19 vaccination.

GSK, in collaboration with CureVac, are conducting this Phase 1 clinical study with the aim of evaluating the second-generation SARS-CoV-2 improved vaccine in a booster vaccination setting. This study will evaluate the CV2CoV mRNA vaccine over a range of dose levels and adult age groups.

1.2 Risk/Benefit Considerations

Detailed information about the known and expected risks and benefits and reasonably expected AEs of the CV2CoV vaccine is provided in the IB. A high-level summary is provided here.

Participants are not expected to directly benefit from study participation. However, their participation in this study will contribute to generating information regarding the vaccine platform being evaluated and the potential for this construct to be further evaluated in Phase 2 and 3 clinical trials.

Due to the lack of experience in human participants, there is currently not enough information available about the relationship of AEs and the administration of the CV2CoV mRNA investigational vaccine.

As for any vaccine, local (eg, pain, swelling, erythema at the injection site) and systemic (eg, fatigue, headache, myalgia) postvaccination symptoms may occur within the first 3 days of vaccination, and are anticipated to resolve within a few days of onset.

Important potential risks for the CV2CoV mRNA investigational vaccine are the following:

- Hypersensitivity reactions, including anaphylaxis.
- Myocarditis.
- Pericarditis.
- Syncope and vasovagal reactions to injection.
- Vaccine-associated disease enhancement is an important risk for all SARS-CoV-2 vaccines.

To mitigate these important potential risks, the following risk strategies have been implemented in the study:

- All participants will remain under observation at the vaccination center for at least 60 minutes after vaccination.
- Participants with history of hypersensitivity or severe allergic reaction to any previous vaccine or any component of the IP 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.
- Participants at increased risk of myocarditis or pericarditis and participants with history of myocarditis or pericarditis are excluded from the study enrolment.
- Participants will be instructed (via the informed consent form) to be alert to symptoms of myocarditis or pericarditis and to contact the study site immediately if occurrence of any of these symptoms.
- As syncope and other anxiety-related reactions may occur before vaccination, the decision to vaccinate the participant will be depending on the clinical judgment of the investigator.

- Participants with medically documented risk factors for severe COVID-19 disease will be excluded from the study and the occurrence of 2 cases of severe COVID-19 disease will trigger the hold of the whole Phase 1 study.

Participants will receive close medical supervision and medical assessments (eg, laboratory testing) during the study.

The investigational CV2CoV vaccine is currently in an early stage of clinical development and vaccine efficacy, immunogenicity, and safety have not yet been demonstrated in humans. Considering the risk mitigation strategies, measures taken, and planned to be taken to minimize risk to participants in this Phase 1 clinical trial, the potential risks associated with the investigational vaccines are considered acceptable.

2 Study Objectives and Endpoints

The study objectives and endpoints are described in Table 2-1.

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary – Safety	
To evaluate the safety and reactogenicity of CV2CoV at each dose level in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• Percentage of participants with MAAEs, SAEs, and AESIs from study vaccination through the end of the study (approximately 180 days after the study vaccine administration), each summarized separately • Percentage of participants with each solicited local and systemic AE within the 7-day postvaccination period (Days 1 to 7) • Percentage of participants with unsolicited AEs up to 28 days after study vaccination, including clinically relevant abnormal laboratory findings
Secondary – Immunogenicity	
To explore the dose response and effect of CV2CoV at each dose level on neutralizing Ab titers against pseudovirus bearing spike protein from SARS-CoV-2 WT in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• GMTs of neutralizing Ab titers against pseudovirus bearing spike protein from either SARS-CoV-2 WT at each collection time point (Days 1, 8, 15, 29, 85, and 180) • Percentage of participants with seroresponse (≥4-fold rise from baseline) at Day 29 after the booster dose • GMI from baseline of neutralizing Ab titers against pseudovirus bearing spike protein from SARS-CoV-2 WT at each collection time point (Days 8, 15, 29, 85, and 180)
To describe serum-binding Ab (IgG) levels specific for vaccine antigens in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• GMTs of binding IgG against SARS-CoV-2 S protein and RBD at each collection time point (Days 8, 15, 29, 85, and 180) • GMI from baseline of binding IgG against SARS-CoV-2 S protein and RBD at each collection time point (Days 8, 15, 29, 85, and 180)

Objectives	Endpoints
Tertiary Objectives	
CCI [redacted]	

3 Investigational Plan

3.1 Study Design

This Phase 1 study will evaluate the safety, reactogenicity, and immunogenicity of the CV2CoV vaccine in SARS-CoV-2 seropositive healthy adult participants. The study will be conducted in 5 sequential cohorts with dose escalation from 2 µg to 20 µg. A total of up to approximately 180 healthy adult participants will be enrolled, 30 per dose group as indicated in Table 3-1. The 30 participants will be distributed between the younger (≥18 to <65 years old) and older (≥65 years old) age groups, with a minimum of 10 and a maximum of 20 participants in each age group. There will be 3 sentinel participants in each age group within each dose group. A study design schematic is provided in Figure 3-1.

Table 3-1 CV2CoV Study Cohorts, Dose Groups, and Dose Levels

Cohort	Dose Group	Dose Level	Younger Adults ≥18 to <65 Years of Age	Older Adults ≥65 Years of Age	Total Dose Group Sample Size
1	1a	2 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
	1b	4 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
2	2	8 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
3	3	12 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
4	4	16 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
5	5	20 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30

Note: The first 3 participants enrolled in each age group within each dose group will be sentinel participants.

The screening period will be up to 14 days, study vaccine administration will occur on Day 1, and participants will have approximately 180 days (6 months) of follow-up after study vaccine administration. Study assessments will be performed in an outpatient setting at qualified study sites.

The study will be open-label. Participants in all cohorts will be screened for eligibility up to 14 days before enrollment. Participants will receive study vaccine according to their cohort (Table 3-1), dose group, and age group; and study visits will proceed according to the SOE (Table 13-1). Participants will be sequentially enrolled to the dose level assigned to their cohort.

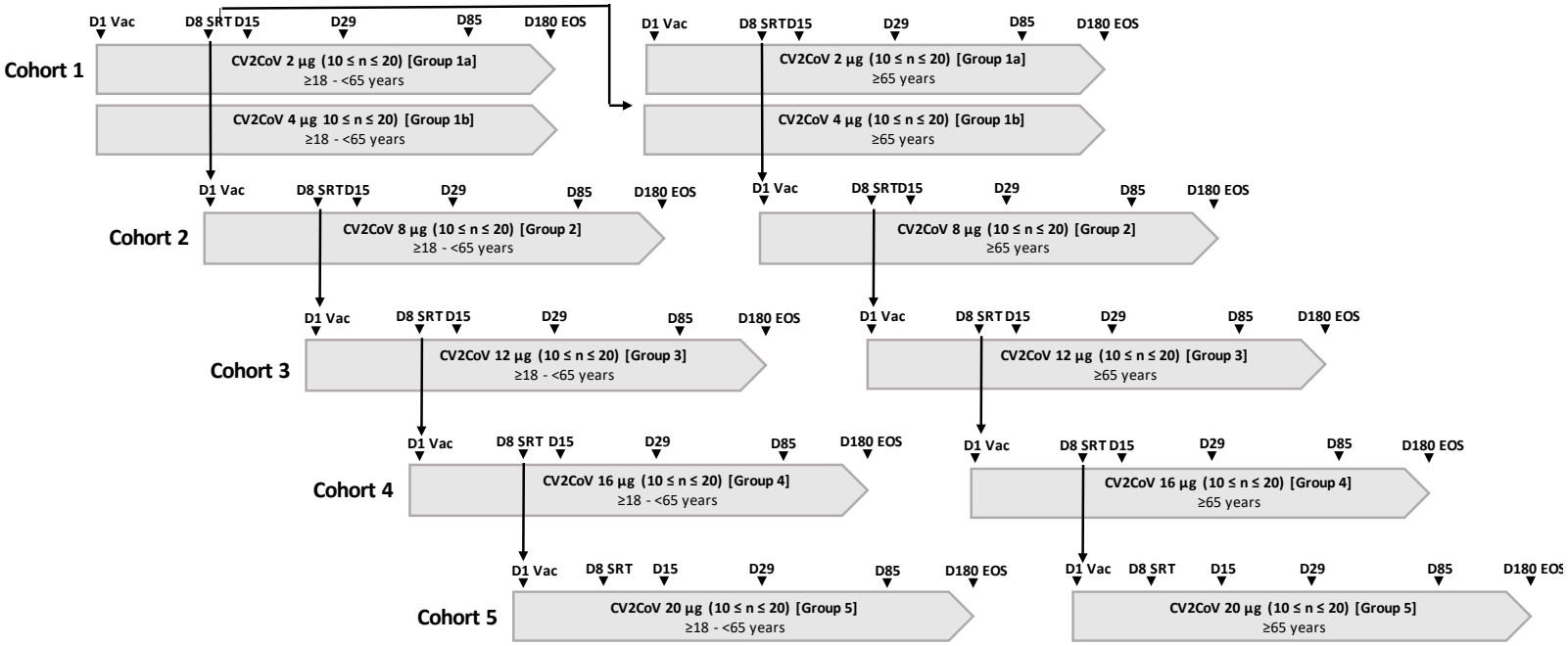
Enrollment in each dose cohorts and the progression from vaccination in younger to older adult participants will be staggered based on SRT data review will progress as described in Section 7.8. Holding rules for dosing are described in Section 5.9.

Three sentinel participants in the younger age group (Cohort 1) will be enrolled before opening enrollment to the older age group (Cohort 1). Study vaccine administration must be separated by at least 20 hours between sentinel participants in all cohorts and all dose groups. Sentinel participants will remain on site for approximately 4 hours after study vaccination and the remainder of participants in each group will remain on site for approximately 60 minutes after study vaccination for safety monitoring. A safety follow-up telephone call to each sentinel participant in each dose group will be performed on Day 2 (at least 20 hours postvaccination). Vaccination of the next sentinel participant will proceed, provided the safety was acceptable for the prior sentinel(s) per investigator's assessment.

Escalation to the next higher dose cohorts will be based on the SRT review of safety data from the same age group. Enrollment into Cohorts 2 and 3 (8 and 12 µg, respectively) will begin after the SRT has reviewed Days 1 to 8 safety data (including Day 8 laboratory data) from 3 sentinel participants from the previous dose cohort. Enrollment into Cohorts 4 and 5 (16 µg and 20 µg, respectively), will begin after the SRT has reviewed Days 1 to 8 safety data from all participants in the previous dose cohorts.

A first interim analysis of safety and immunogenicity data up to 14 days after study vaccine administration in participants enrolled in Cohorts 1, 2, and 3 will be performed. A second interim analysis of safety and immunogenicity data will be performed 14 days after participants in Cohorts 4 and 5 have received study vaccine.

Figure 3-1 Study Design Figure



3.2 Rationale for Study Design

This is a Phase 1 first-time-in-human study designed to evaluate the safety, reactogenicity, and immunogenicity of the GSK-CureVac second-generation CV2CoV vaccine to prevent COVID-19 disease caused by existing and new emerging strains of the SARS-CoV-2 virus. This study will evaluate the CV2CoV vaccine in a booster vaccination setting. The study comprises an adult population of participants who have received a documented full primary vaccination series (2 doses only) with a licensed or authorized mRNA COVID-19 vaccine (only Moderna or Pfizer vaccines). The second-generation vaccines are based on the first-generation CVnCoV vaccine, for which efficacy and safety data have been collected in the ongoing Phase 2b/3 study (NCT04652102). The rationale for evaluation of doses from 2 to 20 µg is based on the following: 1) The data from this study will support decisions as to whether the candidate vaccine should be further evaluated in advanced phase clinical trials. 2) The data from this study will guide dose selection. 3) The proposed study will support development of the platform. Specifically, if the CV2CoV monovalent candidate induces robust immune responses with an acceptable safety profile, there may be potential to develop future multivalent vaccines to prevent COVID-19 disease based on this platform. The rationale for including older adults in this study is because this age group is at increased risk for severe COVID-19. In addition, the efficacy of the CVnCoV vaccine was lower in older adults than in younger adults < 65 years of age. Thus, safety and immunogenicity data on CV2CoV in this age group will be critical to guiding decisions on whether the CV2CoV vaccine candidate should be advanced further in development.

The starting doses of the CV2CoV vaccine are 2 µg and 4 µg in Cohort 1. These starting doses are based on previously tested doses for the first-generation CVnCoV vaccine.

The maximum planned dose of the CV2CoV vaccine is 20 µg in the present study. In the Phase 1 study, the reactogenicity profile of the first-generation CVnCoV vaccine was dose-dependent from 2 µg to 20 µg. Solicited reactions were more commonly systemic with a frequency of reports generally similar after the administration of the first and the second dose (except for 8 µg and 16 µg). The severity of systemic solicited events increased with dosages with an overall rate of CCI [redacted] of participants reporting a Grade 3 event. However, Grade 3 solicited events were mostly short-lived and self-limiting, eg, Grade 3 AEs CCI [redacted] only lasted for 1 day and, 1 participant CCI [redacted] reported a Grade 3 myalgia after the second dose for 3 consecutive days and resolved on the fourth day. Adherence of participants

to administration of the second dose remained very high, even for the higher doses. Until 24 October 2021, no vaccine-related SAEs, AESIs, or fatalities were reported for any dose in the Phase 1 study. Increases in frequency or severity were not observed for Grade 3 solicited AEs in the later clinical phases with larger sample sizes.

Risk to study participants will be mitigated in several ways:

1) A stagger will occur between the younger and older adults based on SRT review of Days 1 to 8 safety data (including Day 8 laboratory data) from 3 sentinels (Cohort 1).

2) Each sentinel will be called at Day 2 (at least 20 hours postvaccination) to monitor their safety postvaccination prior to vaccination of the next sentinel.

3) The SRT will review Days 1 to 8 safety data (including Day 8 laboratory data) from 3 sentinels in each dose cohort (Cohorts 1-5) prior to expansion in the same dose cohort.

4) The SRT will review Days 1 to 8 safety data (including Day 8 laboratory data) from 3 sentinels prior to escalation to the next higher dose cohort (Cohorts 1-3).

5) The SRT will review data from the entire dose cohort prior to escalation to the next higher dose cohort (Cohorts 4-5).

6) The SRT will continue to review all available safety data to determine study progression.

7) Study holding rules have been specifically predefined so that the study will be fittingly put on hold pending the review of all accumulated safety data by the SRT and to decide whether expansion of vaccination and escalation through the higher dosages may continue.

Participants will be monitored for 6 months after receiving study vaccine on Day 1. Safety monitoring, including physical examinations, clinical laboratory assessments, vital sign measurements, and AEs (solicited and unsolicited AEs, SAEs, MAAEs, and AESIs), will be performed throughout the study via outpatient site visits and participant eDiary completion. Due to the ongoing pandemic, safety follow-up visits may be completed via televisits, as permitted by country regulations. In-person visits should be maintained in the study unless

there is a public health emergency limiting access to study sites. During such an emergency or extenuating circumstance, televisits can be employed to keep personal access to subjects and ascertain their safety at a high level.

Refer to the IB for nonclinical data for the CV2CoV vaccine. Refer to Section 1.2 for risk-benefit considerations.

4 Participant Selection and Withdrawal Criteria

4.1 Selection of Study Participants

A total of up to approximately 210 healthy adult participants (approximately 90 younger adults [≥18 to <65 years of age] and approximately 120 older adults [≥65 years of age]) will be enrolled in the study. Participants will be assigned to study vaccine only if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each participant must meet all the following criteria to be enrolled in this study:

1. Must provide documented informed consent prior to any study procedures being performed.
2. Is capable of understanding and agrees to comply with planned study procedures and to be available for all study visits, including being willing and able to use electronic devices during the study.
3. Has received at least 2 doses of Pfizer-BioNTech (Comirnaty®) or Moderna (Spikevax®) mRNA COVID-19 vaccine, with the last dose of vaccine received at least 6 months prior to Screening and has provided documentation of receiving the vaccination series (eg, vaccination card).
4. Negative for SARS-CoV-2 infection by RT-PCR test at Screening.
5. Is a male or nonpregnant female 18 to <65 years of age (younger adult group) or ≥65 years of age (older adult group) at Screening.
6. Has a body mass index of 18 to 34.9 kg/m^2, inclusive, at Screening.
7. If the participant is a WOCBP, as described in Section 13.2, the participant agrees to practice true abstinence or use at least 1 highly effective form of contraception for at least 30 days prior to study vaccination up to 3 months after study vaccination.
8. Agrees to refrain from blood or plasma donation from Screening and throughout the end of the study.
9. Is healthy or medically stable as determined by medical history, clinical laboratory tests, vital sign measurements, and physical examination findings, as determined by investigator judgment.

4.1.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Participant is female and has a positive serum pregnancy test result at Screening or plans to become pregnant during the study.
2. Participant is female and is breastfeeding or plans to breastfeed from study vaccination to 3 months after study vaccination.
3. Has any clinically significant abnormal biochemistry or hematology finding (defined as ≥Grade 1; Section 6.1.2) at Screening. Note: Older adults (aged ≥65 years) with Grade 1 laboratory abnormalities which have been stable for at least 6 months prior to enrollment may be included in the study.
4. Has any medical disease or condition that, in the opinion of the investigator, precludes study participation. This includes any acute, subacute, intermittent, or chronic medical disease or condition that would place the participant at an unacceptable risk of injury, render the participant unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the participant's successful completion of the trial.
5. Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (eg, malignancy) or immunosuppressive/cytotoxic therapy (eg, medications used during cancer chemotherapy, organ transplantation, or to treat autoimmune disorders).
6. 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, persistent myocardial viral infection (eg, due to enterovirus or adenovirus), and celiac disease.
7. [Edited and moved to exclusion criterion 24i]
8. Has an acute febrile illness with a temperature ≥38.0°C or ≥100.4°F observed by the participant or at the study site within 72 hours prior to study vaccination. Participants with suspected COVID-19 symptoms (Section 6.6) should be excluded and referred for medical care.

9. Has a prior confirmed diagnosis of chronic hepatitis B, hepatitis C, or HIV 1/2 infection or evidence of active infection at Screening.
10. Has participated or plans to participate in another investigational study involving any investigational drug or device within 60 days or 5 half-lives, whichever is longer, before study vaccination and throughout the end of the study.
11. Has previously participated in another investigational vaccine study with investigational vaccine administered within 6 months of study vaccination.
12. Has received or plans to receive any licensed vaccine within 4 weeks before or after study vaccination. Inactivated vaccines for influenza are permitted during the study if they are administered at least 14 days before or after study vaccination.
13. Is planning to receive an authorized or licensed COVID-19 booster vaccination for the duration of the study (for adults who are not covered by local recommendations to receive booster per current standard of care) OR
    Is planning to receive an authorized or licensed COVID-19 booster vaccination on or before Day 29 of the study (for adults covered by local recommendations to receive booster).
14. Has received or plans to receive immunoglobulins or any blood or blood products within 90 days before study vaccination and throughout the study.
15. Has a history of hypersensitivity or severe allergic reaction, including anaphylaxis, generalized urticaria, angioedema, and other significant reactions to any previous vaccine or any component of the IP.
16. Has a history of hypersensitivity or severe allergic reaction (including anaphylaxis, generalized urticaria, angioedema, and other significant reactions) to beta lactam antibiotics.
17. Reports chronic use (more than 14 continuous days) of any medication that may be associated with changes in immune function including, but not limited to, systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulins, interferons, immunomodulators, cytotoxic drugs, or other similar or toxic drugs within 6 months of study vaccination. Note: The use of low-dose topical, ophthalmic, inhaled, and intranasal steroid preparations is permitted.

18. Has a bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising after IM injections or venipuncture.
19. Has a history of alcohol abuse or other recreational drug use (excluding cannabis) within 6 months before study vaccination.
20. Has any abnormal skin condition or permanent body art (eg, tattoo) that would interfere with the ability to observe local reactions at the study vaccination injection site.
21. Has had known close contact with anyone who had a confirmed SARS-CoV-2 infection within 14 days before study vaccination.
22. Participant is an employee or family member of the investigator or study site personnel.
23. Has any self-reported or medically documented significant medical or psychiatric condition. Significant medical conditions include, but are not limited to, the following:
    a. Moderate or severe respiratory disease (eg, chronic obstructive pulmonary disease, asthma)
    b. Uncontrolled hypertension, defined as an average systolic blood pressure ≥140 mmHg for participants ≤60 years old, and ≥150 mmHg for participants >60 years old, or a diastolic blood pressure ≥90 mmHg for any age
    c. Significant cardiovascular disease (eg, congestive heart failure, cardiomyopathy, ischemic heart disease) or history of myocarditis or pericarditis
    d. Neurological or neurodevelopmental conditions (eg, Down's syndrome, dementia, chronic migraine not controlled by medication, epilepsy, stroke, or seizure in the last 3 years, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis, or transverse myelitis)
    e. Ongoing malignancy or recent diagnosis of malignancy in the last 5 years (excluding basal cell and squamous cell carcinoma of the skin)
    f. Tuberculosis or nontuberculosis mycobacterial infection
    g. Autoimmune disease, including hypothyroidism without a defined nonautoimmune cause

h. Immunodeficiency of any cause, including from solid organ transplant, blood or bone marrow transplant, use of corticosteroids, or use of other immune-weakening medicines

i. Type 1 or 2 diabetes mellitus regardless of disease control

24. Has any of the following self-reported or medically documented risk factors for severe COVID-19:

a. Cancer

b. Chronic kidney disease

c. Sickle cell disease

d. Cerebrovascular disease

e. Cystic fibrosis

f. Chronic liver disease

g. Pulmonary fibrosis

h. Thalassemia

i. Smoking or other inhaled substance use, including tobacco, cannabis, or nicotine vapors, with an average of ≥5 cigarettes a day or equivalent (currently or within 1 year of Screening).

25. Has a history of documented SARS-CoV-2 infection or COVID-19 within 6 months before Screening.

4.1.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number. A maximum of one rescreen is allowed.

Participants who are rescreened are required to sign a new ICF prior to undergoing rescreening assessments.

4.2 Discontinuation From Study Vaccine and/or Withdrawal From the Study

As this is a single dose booster vaccination study, discontinuation from IP does not apply; however, participants may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep participants in the study for follow-up evaluations. The reasons for participants withdrawing from the study will be recorded.

Participants will be informed of any authorized or licensed booster vaccines available for COVID-19 during the study to support an informed choice for whether to continue or discontinue participation in the study.

A participant may withdraw or be withdrawn from the study for any of the following reasons:

1. The participant does not meet the protocol inclusion or exclusion criteria.
2. The participant is noncompliant with the protocol.
3. The participant has a serious or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study.
4. The participant has safety laboratory results that reveal clinically significant hematological or biochemical changes from the baseline values, per investigator judgment.
5. The participant has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal. Note: Such events should also be reported as AEs.
6. The participant is lost to follow-up.
7. Other reasons (eg, pregnancy, development of contraindications of use of the IP).
8. The participant withdraws consent, or the investigator or sponsor decides to discontinue their participation in the study.

4.2.1 Discontinuation From Study Vaccine

Only a single dose booster vaccination will be administered to each participant; thus, discontinuation from study vaccine is not applicable.

4.2.2 Withdrawal From the Study

If a participant withdraws or is withdrawn from the study, the ET procedures as indicated in the SOE (Table 13-1) should be completed.

The investigator will also withdraw a participant if the sponsor terminates the study.

4.2.3 Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 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.

If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

4.2.4 Replacements

Participants who withdraw may be replaced at the discretion of the sponsor after consultation with the SRT. In particular, any participants who are assigned to a group in error and not

vaccinated may be replaced. In general, participants who withdraw for reasons connected to the study vaccine (eg, safety concerns after study vaccination) should not be replaced.

5 Study Vaccines

5.1 Method of Assigning Participants to Study Vaccine Groups

Participants will receive study vaccine on Day 1 according to a specific cohort, dose group, and age group. Interactive response technology will be used to track enrollment. Biostatistics will generate the treatment schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IRT, which will link sequential participant numbers to treatment codes. Note: If a participant is consented electronically, a participant number may be generated; however, that number will be updated to align with the IRT number after enrollment is complete for consistency in each participant's study records.

5.2 Study Vaccines Administered

Study vaccine will be administered on Day 1. Study vaccine will be administered as a single IM injection of 0.3 mL in the deltoid area, preferably in the nondominant arm.

Refer to the IB and Pharmacy Manual for further details regarding the study vaccine preparation and administration.

5.3 Identity of Investigational Product

Investigational product refers to the CV2CoV vaccine that will be administered during the study.

CCI [redacted] The diluent composition for CV2CoV is 0.9% sodium chloride.

GSK Biologicals SA and/or CureVac will provide adequate supplies of IP to PPD for distribution to the study sites. The following IP will be used in the study:

Table 5-1 Investigational Product Information

Description	Investigational Product CV2CoV[a]
CCI [redacted]	CCI [redacted]
CCI [redacted]	WT CCI [redacted]
CCI [redacted]	CCI [redacted]

a. Product reference: CV07050201.
b. CCI [redacted]

The LNP encapsulated mRNA product, CV2CoV, is supplied in glass vials as a sterile colloidal dispersion in a frozen liquid formulation. A diluent will be used to dilute the products to the appropriate dose levels.

Refer to the Pharmacy Manual for any details regarding blinding requirements, storage, and preparation for the IP.

5.4 Management of Clinical Supplies

5.4.1 Investigational Product Packaging and Storage

Investigational product will be supplied in vials that will require further dilution and preparation procedures; please refer to the Pharmacy Manual for additional packaging and preparation details. The IP must be stored in a secure, restricted freezer and kept at the temperature noted in the Pharmacy Manual at each stage of preparation for IM administration.

Once prepared and diluted for IM administration, refer to the Pharmacy Manual for storage conditions. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

Refer to the Pharmacy Manual for further details regarding storage and preparation requirements.

5.4.2 Investigational Product Accountability

The investigator will maintain accurate records of receipt of all IP, including dates of receipt. In addition, accurate records will be kept regarding when and how much IP is administered to each participant in the study. Only participants enrolled in the study may receive the IP and only authorized site personnel may supply or administer the IP. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all IP will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused IP are provided in the Pharmacy Manual.

5.4.3 Other Supplies

Refer to the Pharmacy Manual for ancillary formulation preparation or injection materials that will be distributed by PPD to the study sites or that the study sites will need to procure.

5.5 Overdose Management

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

There is no specific treatment recommended for an overdose.

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

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 3 days.
3. Document the quantity of the excess dose in the eCRF.

Decisions regarding any overdoses will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

5.6 Blinding

Participants will receive study vaccine as described in Section 5.1. The study will be open-label. The laboratories responsible for immunogenicity analyses will be blinded.

In the event of a quality assurance audit, auditors will be allowed access to study vaccine records at the study sites to verify that dispensing was performed accurately.

A statistical and programming team may perform interim analyses during the study. Unblinded safety and immunogenicity summaries, if applicable, will be provided to the SRT to inform study decision for progressing enrollment (Section 7.8).

5.7 Compliance With Study Vaccine

All participants will be vaccinated at the study site by the investigator or designee, under medical supervision. The date and time of study vaccine administration will be recorded in the source documents and in the eCRF. The dose of study vaccination and participant

identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study vaccination.

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site personnel.

5.8 Prior, Concomitant, and Rescue Medications, Vaccines, and Therapies

5.8.1 Prior and Concomitant Medications

Use of all prior and concomitant medications (within 6 months of Screening) and vaccinations (within 18 months of Screening) will be recorded in the participant's eCRF. The minimum requirement is that drug name and the dates of administration are to be 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 vaccination should also be recorded in the participant's eCRF. Any changes in concomitant medications also will be recorded in the participant's eCRF throughout the study.

5.8.2 Allowed Concomitant Therapy

Any concomitant medication 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 are recorded in full in the eCRF.

The following concomitant therapies are allowed during the study:

- Acetaminophen/paracetamol
- Contraception, as described in Appendix 13.2
- Low-dose topical, ophthalmic, inhaled, and intranasal steroid preparations
- Local intra-articular steroids that are expected to remain localized in the joint space in which they are administered
- Inactivated influenza vaccines are allowed if received at least 14 days before or after study vaccination. Note: If other nonstudy vaccines are received during the study, participants may continue to complete the remaining study assessments. Any impact on the immunogenicity data will be addressed in the data analysis.

- Participants may take concomitant medications for management of medically stable chronic conditions as long as the medication and medical conditions are not exclusionary (Section 4.1.2)

Participants will be allowed to receive a booster dose of a licensed or authorized (conditional regulatory approvals, including emergency use authorizations are acceptable) COVID-19 vaccine, per national recommendations, if received after the Day 29 visit.

No concomitant medications will be provided by the sponsor or PPD.

5.8.3 Rescue Medicine

There are no known rescue medications for the IP; supportive care should be provided to participants.

5.9 Study Holding Rules

The study holding rules in Table 5-2 will be applied independently to each dose group.

Table 5-2 Study Holding Rules

Study Holding Rule	Study Holding Rule Description	Number of Participants Needed to Trigger a Study Hold
1a	Death or any life-threatening SAE regardless of causality	≥1
1b	Any non-life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per investigator or Sponsor assessment	≥1
1c	Any withdrawal from the study (by investigator or participant request) following a Grade 3 AE	≥1
1d	Any local or general solicited AE leading to hospitalization OR necrosis at the injection site; each with an event onset within the 7-day postvaccination period (Days 1 to 7)	≥1
1e	Severe cases of SARS-CoV-2 infection	≥2
1f	Any same or similar Grade 3 related unsolicited events**,** including but not limited to the identical MedDRA high-level term	≥2
1g	Same Grade 3 solicited local or systemic AE in an investigational group	>3
1h	Same Grade 3 or above abnormality in prespecified hematological or biochemical laboratory parameters with an event onset by Day 8 (± 1 day) postvaccination, except nonclinically significant lymphopenia	≥3
2a	Any Grade 3 solicited events in an investigational group, with an event onset within the 7-day postvaccination period (Days 1 to 7)	2 out of 3 first exposed participants 3 out of 5 first exposed participants 7 out of 16 first exposed participants 9 out of 22 first exposed participants 11 out of 28 first exposed participants 12 out of 30 first exposed participants (combined younger and older adult age groups)
2b	Any **Grade 3 unsolicited AE**, that can be reasonably attributed to the vaccination as per Investigator or Sponsor assessment, with an event onset within the 7-day (Days 1 to 7) postvaccination period	2 out of 15 first exposed participants 3 out of 30 first exposed participants (combined younger and older adult age groups)

Study holding rules 1a through 1d will be assessed by the investigators on a continuous basis. Study holding rules will lead to a halting of the entire study, with the exception of study

holding rule 1c, which will lead to halting of the concerned cohort and the next cohorts with higher doses.

Study holding rules 1e, 1f, 1g, 1h, 2a and 2b will be assessed by the SRT on an ongoing basis. An adaptive Bayesian logistic regression model will be used during SRT meetings (scheduled or ad-hoc according to Table 5-2) to evaluate the posterior probability for the percentage of severe solicited AEs at the current and the next dose (Appendix 13.3). A lower than 50% posterior probability, that the percentage is above the maximal tolerable dose, will be favorable to progress at the next dose. Each study holding rule will be applied per cohort and age group. Based on the historical Phase 1 data from CVnCoV, Moderna and Pfizer mRNA COVID vaccines, the maximum tolerable rate has been set up to 30%.

The SRT will review all available safety data at scheduled time points and at the time when any of the study holding rules are met. A recommendation will be made to the sponsor on whether a cohort or group should be permanently stopped, modified, or continued unchanged. If a study holding rule is met, it will be escalated according to process to the SRT who will decide whether other participants can be enrolled/vaccinated. Medical judgment, taking into account all available safety data at the time of review, should be the basis for decision to continue the study or not.

In the event of a halting of the study, ethical and regulatory authorities will be notified per local requirements.

6 Study Assessments and Procedures

Before any study procedures are performed, all potential participants will be consented using an IRB/IEC-approved ICF. Additional procedural details related to the ICF are provided in Section 9.3. Study assessments will be performed in an outpatient setting at qualified study sites. Due to the ongoing pandemic, safety follow-up visits may be completed via televisits, as permitted by country regulations. In-person visits should be maintained in the study unless there is a public health emergency limiting access to study sites. During such an emergency or extenuating circumstance, televisits can be employed to keep personal access to subjects and ascertain their safety at a high level.

Refer to the SOE table in Appendix 13.1 for a full list of visits and assessments (Table 13-1).

A maximum of 150 mL of blood will be collected per participant per visit. This may include 50 mL of blood collected at 2 visits for participants enrolled at sites where PBMCs are collected (ie, cell-mediated immunity subset). The maximum amount of blood collected over the 6-month duration of the study is approximately 800 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

6.1 Safety and Reactogenicity Assessments

Safety will be assessed through the collection and evaluation of solicited and unsolicited AEs, MAAEs, SAEs, and AESIs. Safety will also be assessed based on physical examinations, vital sign measurements, and clinical laboratory assessments. Refer to the SOE table in Appendix 13.1 for assessment time points and a full list of visit and assessments (Table 13-1).

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

Any abnormal laboratory test results or other safety assessments (eg, physical examinations, vital sign measurements), including those that worsen from baseline or are clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs as applicable.

6.1.1 Adverse Events

6.1.1.1 Definitions

6.1.1.1.1 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the IP or their clinical significance.

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to the IP. Participants will be instructed to contact the investigator at any time after enrollment if any symptoms develop.

A solicited AE is defined as an AE that is reported with onset within 7 days of study vaccination (Days 1 to 7), as recorded by participants in an eDiary (Section 6.1.1.5). After study vaccination all participants will be instructed to record selected local and systemic postvaccination reactions (solicited AEs) in an eDiary. Local solicited AEs will include injection site pain, redness, swelling, and lymphadenopathy. Systemic solicited events will include fever, headache, fatigue, myalgia, arthralgia, and chills. Solicited local and systemic AEs will be used to assess reactogenicity and will be assigned a grade as described in Section 6.1.1.2.1. Any such AEs reported after the 7-day window will be reported as unsolicited AEs.

An unsolicited AE is defined as any AE that is volunteered from the participant and occurs within 28 days after vaccination.

An MAAE is defined as an AE that results in a visit to a medical professional. Medically attended visits are defined as a telemedicine visit, physician’s office visit, urgent care visit, emergency room visit, hospitalization, or death.

6.1.1.1.2 Serious Adverse Events

An SAE is defined as any event that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a spontaneous miscarriage (see also Section 6.2)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.1.1.1.3 Suspected Unexpected Serious Adverse Reactions

A SUSAR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IP).

6.1.1.1.4 Adverse Events of Special Interest

An AESI (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate (ICH E2F; CIOMS VI).

For this study, AESIs will include the following events:

- Virologically confirmed SARS-CoV-2 infections (see Section 6.6 for disease definitions)
- Potential immune-mediated disorders (Appendix 13.4)
- Anaphylaxis or severe hypersensitivity within 24 hours after study vaccine administration
- Pericarditis or myocarditis

Refer to Section 6.1.1.3.1 for reporting AESIs.

6.1.1.2 Eliciting and Documenting Adverse Events

Adverse events will be reported throughout the study. Nonserious AEs will be reported from the time of the administration of IP until 28 days after the administration of IP; SAEs will be reported from the time the participant signs the ICF until exit from the study.

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IP, the investigator must notify PPD Pharmacovigilance within 24 hours of learning of the event (Section 6.1.1.3.1).

At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being.

In addition to participant observations, AEs identified from any study data (eg, laboratory values, physical examination findings) or identified from review of other documents (eg, participant eDiaries) that are relevant to participant safety will be documented on the AE page in the eCRF.

As described in Section 6.1.1.1.1, participant eDiaries will be used to collect solicited AEs.

6.1.1.2.1 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities.

Solicited AEs will be graded in intensity by the participant. The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs, including SAEs, recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity of the following solicited events will be assessed as described in Table 6-1.

Table 6-1 Intensity Scales for Solicited Symptoms

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 and does not interfere with activity
	2	5.1 – 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
Lymphadenopathy[a]	0	None
	1	Mild: No interference with activity
	2	Moderate: Some interference with daily activity
	3	Severe: Prevents daily activity
Temperature[b]	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
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

a. Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the vaccination arm.

b. Refer to Section 6.1.4 for the definition of fever.

The intensity of AEs will be assigned to one of the following categories:

- 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.

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as "serious" when it meets one of the predefined outcomes (Section 6.1.1.1.2).

Refer to Section 13.5 (Appendix 5) for grading of laboratory-associated AEs.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.1.1.2.2 Assessment of Causality

The investigator's assessment of an AE's relationship to the IP is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the IP in causing or contributing to the AE will be characterized using the following classification and criteria:

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

6.1.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes, but is not limited to, the following:

- Event term
- Investigator-specified assessment of severity and causality to IP
- Seriousness/grade
- Time of onset of the event
- Time of resolution of the event
- Any required treatment or evaluations
- Outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

6.1.1.3.1 Reporting Serious Adverse Events and Adverse Events of Special Interest

Any AE that meets SAE criteria (Section 6.1.1.1.2) must be reported to PPD Pharmacovigilance within 24 hours after site personnel first learn of the event. Events should be captured electronically in the EDC system; however, if the EDC is unavailable, a backup paper option is available and this form can be faxed to the fax number listed below.

SAE Hotline: **+1-800-201-8725**
Fax: **+1-888-488-9697**

Any AE that meets AESI criteria (Section 6.1.1.1.4) must be reported to PPD Pharmacovigilance within 24 hours after site personnel first learn of the event.

If the EDC is unavailable and a faxed form is used to report an SAE or AESI, the site should update the EDC with exactly the same information reported on paper (by fax) as soon as possible after the EDC becomes available again.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information from the sponsor will review and then file it as appropriate and will notify the IRB/IEC according to local requirements.

6.1.1.3.2 Reporting Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRB/IECs, and applicable health authorities based on applicable legislation.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

6.1.1.4 Follow-Up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered to be stable, or the participant is lost to follow-up.

6.1.1.5 eDiary

An eDiary will be used after study vaccination to record solicited local injection site and systemic AEs, body temperature, and any concomitant medications during 7 days after study vaccination (Days 1 to 7) for reactogenicity assessment. Study site personnel will instruct the participants on use of the eDiary. The site staff will review the eDiary data at Day 8.

Participants will be instructed to contact the study site as needed at any time point during the study with safety concerns. Any AE that meets SAE criteria (Section 6.1.1.1.2) must be

reported to PPD Pharmacovigilance immediately (ie, within 24 hours) after site personnel first learn of the event (Section 6.1.1.3.1).

6.1.2 Clinical Safety Laboratory Assessments

The following laboratory assessments will be performed at the time points specified in the SOE (Table 13-1):

Hematology:	Basophils, eosinophils, erythrocytes (red blood cells), hemoglobin, leukocytes (white blood cells), lymphocytes, monocytes, neutrophils, and platelets
Chemistry:	Bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, and uric acid
SARS-CoV-2:	• SARS-CoV-2 serology (Ab), which will include S and N protein for prevaccination timepoints and N protein for postvaccination timepoints to monitor for undetected SARS-CoV-2 infections • SARS-CoV-2 RT-PCR (nasal swab)
HIV/HBV/HCV	• Hepatitis B surface antigen test • HIV 4th generation antigen/Ab test • Anti-HCV test
Other analyses:	Female participants of childbearing potential: β-human chorionic gonadotropin (serum test at Screening; urine test at additional time points) Serum FSH, to confirm postmenopausal status (Section 13.2)

The clinical safety laboratory assessments will be performed by a local or central laboratory as detailed in the Laboratory Manual. Screening laboratory tests and SARS-CoV-2 RT-PCR may be repeated once for enrollment requirements.

The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). Any clinically relevant laboratory results should be reported as an AE or SAE, as appropriate, using the AE intensity grading (Section 6.1.1.2.1).

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual. If laboratory values from nonprotocol-specified laboratory assessments performed at the local study site laboratory require a change in participant management or are considered clinically significant by the investigator, then the results must be recorded in the eCRF.

6.1.3 Physical Examinations

A complete physical examination including height and weight will be performed at Screening as indicated in the SOE (Table 13-1). Symptom-directed physical examinations will be performed as clinically indicated at subsequent visits.

6.1.4 Vital Signs

Vital sign measurements will be performed at the time points indicated in the SOE (Table 13-1). Vital signs will be measured in a sitting position after at least 5 minutes of rest and will include temperature, pulse, respiration rate, oxygen saturation by pulse oximetry, and systolic and diastolic blood pressure. For participants who have an abnormal blood pressure reading at Screening, blood pressure measurement may be repeated and the blood pressure measurement for eligibility may be based on an average of up to 3 blood pressure measurements, to better assess whether known hypertension is well controlled or to evaluate for undiagnosed hypertension. These assessments can be made on separate visits during the screening period to provide more comprehensive sampling. Self-reported baseline measurements documented in a personal log or from medical records taken on consecutive

days in the week before the screening visit can also be accepted, subject to the investigator´s discretion. Vital sign measurements should be collected before and after study vaccination on Day 1. Vital sign measurements should also be performed before any scheduled blood collection. Per standard clinical practice, vital sign measurements may be repeated per investigator discretion.

Body temperature will be measured throughout the study. Participants who are febrile (temperature ≥38.0°C or ≥100.4°F) before study vaccination should be rescheduled for study vaccination within the relevant window period of Screening.

6.1.5 Sentinel Participant Safety Follow-up Call

A safety follow-up telephone call to each sentinel participant in each dose group will be performed on Day 2 (at least 20 hours postvaccination). Vaccination of the next sentinel participant will proceed, provided the safety was acceptable for the prior sentinel(s) per investigator's assessment.

6.2 Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using the PPD paper pregnancy report form (Section 13.2) faxed to the same fax number as may be used for backup SAE reports (Section 6.1.1.3.1). To ensure participant safety, site personnel must report each pregnancy to PPD within 24 hours of learning of its occurrence. The pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the participant was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the participant has completed the study, and considered by the investigator as possibly related to the study vaccine, must be promptly reported to PPD as described in Section 6.1.1.3.1.

6.3 Pharmacokinetics

Pharmacokinetics will not be assessed in this study.

6.4 Pharmacodynamics and Biomarkers

Pharmacodynamics and biomarkers will not be assessed in this study.

6.5 Immunogenicity Assessments

Immunogenicity evaluations will be performed at sponsor designated laboratories as detailed in the Laboratory Manual.

Blood samples will be collected to evaluate vaccine-induced neutralizing and binding (IgG) Ab levels and cell-mediated immunity as indicated in the SOE (Table 13-1). On Day 1, the immunogenicity sample should be collected *before* study vaccine administration.

Neutralizing Ab levels against pseudovirus bearing spike from SARS-CoV-2 WT, and potentially pseudovirus bearing spike protein from other variants will be measured. Binding Ab IgG levels against SARS-CoV-2 S protein, RBD, N protein (from WT), and SARS-CoV-2 spike antigens (from other variants) will be measured. Antispike (from WT and potentially other variants) T-cell responses will be explored.

At a subset of study sites, PBMC samples will be collected and assessed by ICS assay (Table 13-1) to evaluate, but not limited to, antispike specific T-cell profiles. Additional T-cell parameters may be evaluated.

6.6 SARS-CoV-2 and COVID-19 Disease Assessment and Definitions

Vaccine efficacy will not be evaluated in this study, but all virologically confirmed SARS-CoV-2 infections should be reported by the participant and documented as clinical events as well as AESIs (Section 6.1.1.1.4). Any available isolate genotyping results will also be requested. Participants will be instructed to inform the investigator in the event of a positive SARS-CoV-2 diagnostic test. Clinical serology testing, including N protein, will be performed at Screening, Day 1, Day 85, and Day 180 to monitor for undetected SARS-CoV-2 infections. A nasal (nasopharyngeal or mid-turbinate) swab sample is scheduled for SARS-CoV-2 RT-PCR testing at Screening and Day 1. The screening sampling and SARS-CoV-2 RT-PCR testing must be performed within the 7 days before Day 1.

All participants with suspected COVID-19 are required to have an unscheduled visit for suspected COVID-19. At this visit, participants will undergo the following assessments:

- Medical history
- SARS-CoV-2 RT-PCR (nasal swab [nasopharyngeal or mid-turbinate])
- Physical examination
- Vital sign measurements
- Review of adverse events
- Concomitant medication/vaccination

All participants with confirmed COVID-19 are required to have an unscheduled COVID-19 convalescent visit. At this visit, participants will undergo the following assessments:

- Medical history
- Physical examination
- Vital sign measurements
- COVID-19 evaluation
- Review of adverse events
- Concomitant medication/vaccination

To complete the COVID-19 evaluation, the investigator will review the history of the participants, including medical records to define the severity of COVID-19. Any virologically confirmed cases of SARS-CoV-2 infection or COVID-19 during the study will be assigned one of the following definitions:

Asymptomatic SARS-CoV-2 infection:	Virologically confirmed SARS-CoV-2 by RT-PCR or N protein seroconversion without any of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea
Symptomatic COVID-19:	Virologically confirmed by RT-PCR and include one or more of the following: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea

Severe COVID-19: Laboratory-confirmed SARS-CoV-2 infection with any of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 per minute, heart rate ≥125 per minute, blood oxygen saturation ≤93% on room air at sea level or partial pressure of oxygen/fraction of inspired oxygen <300 mmHg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation)
- Evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit
- Death

The genetic sequence of the spike-encoding gene or the genome of SARS-CoV-2 strains will also be evaluated in relation to the vaccine sequence, when available.

6.7 Genetics

Human genetics will not be assessed in this study.

7 Statistical Considerations

Analyses will be performed by treatment group combining the younger and older adult participants together, unless specified otherwise. Subanalyses may be performed within each age group. For categorical variables, frequencies, and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

7.1 Statistical Hypothesis

There is no hypothesis testing in this study; where statistical methods are applied, the emphasis will be on estimation with 95% CIs.

7.2 Sample Size Determination

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

Approximately 180 participants will be enrolled in this Phase 1 study, with 6 dose-level cohorts each comprising 2 age groups. With 30 participants in each cohort, there is a 78.5% probability to observe at least 1 AE if the incidence rate is 5% and a 95.8% probability to observe at least 1 AE if the incidence rate is 10%. With 30 participants in each cohort, a 10% unevaluable rate for immunogenicity results, and a standard deviation of 0.45 for log_{10}-transformed increase from Day 1, the ratio of the upper limit of a 2-sided 95% CI and the point estimate of GMI is 1.5.

7.3 Analysis Sets

The following analysis sets will be used in the statistical analyses.

- Enrolled Set: All participants who have a signed ICF and were assigned to a group, vaccinated, or had an immunogenicity blood draw.
- Per Protocol Set: The PP set includes all eligible participants who received a dose of study intervention IP per protocol and who have values for predose and Day 29 neutralizing Ab titers against pseudovirus bearing S protein from CCI [redacted] Results from a blood sample deviating from the dosing or blood sampling schedule (Table 13-1) and results from a blood sample after intercurrent conditions that may

interfere with immunogenicity (eg, virologically confirmed SARS-CoV-2 infections or immunosuppressive or immunodeficient conditions) or from participants who received COVID-19 vaccination within 29 days postvaccination will be excluded from the PP set. The analysis will be done according to the dose that participants received at Day 1. The PP set will be used for the immunogenicity analyses.

- Safety Set: All participants who received any IP. All analyses using the Safety Set will group participants according to the study vaccine actually received. The Safety Set will be used for safety analyses.

7.4 Description of Subgroups to Be Analyzed

Subgroup analysis for safety and immunogenicity endpoints may be performed in selected groups and will be described in the SAP.

7.5 Statistical Analysis Methodology

7.5.1 General Considerations

Statistical analysis will be performed using SAS software Version 9.4 or later. Details of the statistical analyses, methods, and data conventions are described in the SAP. No formal significance testing will be performed.

7.5.2 Analysis of the Primary Safety Endpoints

The primary safety endpoints as detailed in Section 2 will be analyzed as described in the SAP. For all safety endpoints, descriptive summary statistics will be provided for the Safety Set. Safety data listings will also be provided and graphical presentations will be considered as needed.

In addition to the planned summary of SAEs throughout the study, any SAEs that are reported will also be summarized within 28 days of study vaccine administration.

7.5.3 Analysis of Secondary Immunogenicity Endpoints

The secondary endpoints detailed in Section 2 will be analyzed as described in the SAP. Listings will be provided and graphical presentations will be considered as needed.

For the immunogenicity endpoints, the GMTs of specific Ab with corresponding 95% CIs at each time point and percentage of participants with seroresponse (≥4-fold rise from baseline)

at Day 29 after the booster dose, and GMI from baseline of specific Ab with corresponding 95% CIs at each postvaccination time point over prevaccination baseline will be provided by dose group. The GMT, the GMI, and their 95% CI in all cohorts will be analyzed using an ANCOVA with treatment and age group as fixed factors and prevaccination baseline value as a covariable.

7.5.4 Analyses of Exploratory Immunogenicity Endpoints

The exploratory endpoints detailed in Section 2 will be analyzed as described in the SAP. For continuous immunogenicity variables, summary statistics, CIs, and interquartile ranges will be provided. Immunogenicity data listings will also be provided and graphical presentations will be considered as needed.

7.5.5 Safety Analyses

Safety and reactogenicity are the primary study objectives; thus, refer to Section 7.5.2 for the analysis description.

7.5.6 Other Analyses

Summary statistical analyses will be provided for demographics and vital signs at baseline. Subgroup analysis for safety and immunogenicity endpoints may be performed in selected groups and will be described in the SAP.

7.6 Handling of Missing Data

Details regarding handling of missing safety, reactogenicity, and immunogenicity data will be described in the SAP.

7.7 Interim Analyses

A first interim analysis of safety and immunogenicity data covering at least neutralizing Ab titers against pseudovirus bearing S protein from [redacted] up to 14 days after study vaccine administration in all participants enrolled in Cohorts 1, 2, and 3 will be performed. A second interim analysis of safety and immunogenicity data will be performed 14 days after participants in Cohorts 4 and 5 have received study vaccine. Details of these interim analyses will be described in the SAP.

7.8 Safety Review Team

The SRT activities and committee formation will be described in a separate SRT charter.

Cohorts 1 and 2

In the Cohort 1, the SRT will review sentinel Days 1 to 8 safety data (including Day 8 laboratory data) for the 2 µg and 4 µg dose in the younger age groups and make recommendations to open the enrollment in the older age group. The SRT will also review sentinel Day 8 safety data for the 2 µg, 4 µg, and 8 µg dose groups and make recommendations to progress to expanded enrollment in the same dose cohort and to begin enrollment in the next higher cohort.

Cohorts 3, 4, 5

The SRT will review sentinel Days 1 to 8 safety data (including Day 8 laboratory data) for the 12 µg, 16 µg, and 20 µg dose groups and make recommendations to progress to expanded enrollment in the same dose cohort. The SRT will review Day 8 safety data for the entire dose group (eg, 12 µg) and make recommendations to begin enrollment in the next higher dose cohort (eg, 16 µg).

The SRT will take into consideration the study holding rules in Section 5.9.

The SRT review based on interim analysis data will be performed as described in the SRT charter.

Based on SRT review and recommendations, dose groups may be dropped at any time during the study if an unfavorable safety profile is observed in that group or based on safety or immunogenicity data from other groups.

8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management. The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include eDiary information, laboratory reports, etc.

Investigative site personnel will enter participant data into an EDC system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using WHODRUG.

After database lock, each study site will receive electronic files of study media (eCRF data) from PPD, including full discrepancy and audit history. Additionally, electronic files of all of the study site’s data from the study will be created and sent to GSK Biologicals SA for storage. PPD will maintain a duplicate copy in their electronic records. In all cases, participant initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before human participation in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

The IRB/IEC approval should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

9.3 Participant Information and eConsent

Documented informed consent, in compliance with regulatory authority regulations and US Title 21 CFR Part 50, shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. Consent may be collected through a digital method or remote solution if allowed by country and site regulations. Informed consent will ideally be obtained via eConsent with a backup paper consent option if needed. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to the IRB/IEC for review and approval before the start of the study. If the ICF is revised during the study, all active participants must be reconsented using the revised form.

Before recruitment and enrollment, each prospective participant will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give consent to participate in the study by signing the ICF via eConsent or a backup paper option. The authorized person obtaining the informed consent also documents this on the ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research (if applicable) and explain/address the exploratory research portion of the study. Participant medical records need to state that documented informed consent was obtained.

For eConsent, the original signed version of the ICF is retained within the eConsent platform, and downloaded versions are provided to the participant and for the investigator records. In the event a backup paper consent is used, the investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the participant.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Data Protection

All personal data collected related to participants, investigators, or any person involved in the study, which may be included in the sponsor's databases, shall be treated in accordance with local data protection law.

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

10.3 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the participant's disease.

10.4 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and Title 21 of the CFR by providing all essential documents.

10.5 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of participants begins.

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

The investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the sponsor.

10.9 Publications and Results Disclosures

During or after completion of the study, the data may be considered for reporting at a scientific meeting, publication in a scientific journal, or other public format. The procedures and timing for reporting at a scientific meeting, publication in a scientific journal, or other public format will be in accordance with GSK policy and the sponsor has final approval authority over all such issues. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript(s) is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

The study administrative structure will include an SRT, contract research organization, third party vendors, laboratories, etc.

11.1 Monitoring

11.1.1 Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the study. The investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit, if conducted on site. Site monitoring is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. The monitor will evaluate study processes based on PPD standards, ICH E6, and all applicable, regulatory guidelines.

Monitoring details describing the strategy (eg, risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring), are provided in the monitoring plan.

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the participants, must be reviewed and approved by the sponsor or designee. Amendments to the protocol (including emergency changes) must be submitted in writing to the investigator's IRB/IEC, along with any applicable changes to the ICF, for approval before participants can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol or to local regulations or ICH GCP guidelines that may or may not result in a significant, additional risk to the participant or impacts the integrity of study data.

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to study participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, where required.

In order to keep deviations from the protocol to a minimum, the investigator and relevant site personnel will be trained in all aspects of study conduct by the sponsor/sponsor representative. This training will occur either as part of the investigator meeting or site initiation. Ongoing training may also be performed throughout the study during routine site monitoring activities.

11.3 Study Termination

Although GSK Biologicals SA has every intention of completing the study, GSK Biologicals SA reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last visit (includes follow-up visit).

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

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the final data are summarized and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications (as applicable) meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the final report, the sponsor will provide the investigator with the summary of the study results. The investigator is encouraged to share a summary of the results with the study participants, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 References

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13 Appendices

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events

	Screening	D1	D2[a]	D8	D15	D29	D85	D180 (EOS)	Early Termination Visit	Unscheduled Visit for Suspected COVID-19[b]	Unscheduled COVID-19 Convalescent Visit[c]
Window	**D–14 to –1**	**0**	**NA**	**±1**	**±3**	**±3**	**±5**	**±7**	**±7**	**NA**	**NA**
Visit	**1**	**2**	**NA**	**3**	**4**	**5**	**6**	**7**	**7**	**NA**	**NA**
Informed consent	X										
Inclusion/exclusion	X										
Reassess study vaccine eligibility[d]		X									
Demographics	X										
Medical history (including vaccination history)	X								X	X	X
Treatment assignment		X									
Pregnancy test[e]	X	X									
Clinical SARS-CoV-2 serology[f]	X	X					X	X	X		
SARS-CoV-2 RT-PCR (nasal swab)[g]	X	X								X	
Physical examination[h]	X	X		X	X	X	X	X	X	X	X
Vital sign measurements[i]	X	X		X	X	X	X	X	X	X	X
Clinical safety laboratory tests[j]	X	X		X							
Blood sample for binding IgG[f, k]		X		X	X	X[i]	X	X	X		
Blood sample for neutralization[f, k]		X		X	X	X[i]	X	X	X		
Blood for PBMC preparation for ICS (subset of participants)		X			X						
Vaccine administration		X									
COVID-19 evaluation[c]											X[l]
Initiate eDiary for solicited AEs		X									
Site staff review of eDiary			X	X							
Adverse events[m]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccination	X	X	X	X	X	X	X	X	X	X	X

Note: Due to the ongoing pandemic, safety follow-up visits may be completed via televisits, as permitted by country regulations. In-person visits should be maintained in the study unless there is a public health emergency limiting access to study sites. During such an emergency or extenuating circumstance, televisits can be employed to keep personal access to subjects and ascertain their safety at a high level.

a. A safety follow-up telephone call to each sentinel participant will be performed on Day 2 prior to the vaccination of the next participant.

b. Required for participants with suspected COVID-19.

c. Required for participants with confirmed COVID-19.

d. Prior to study vaccine administration, participants will be reassessed for development of any new condition that would be considered exclusionary including acute illness, pregnancy, or development of new risk factors for severe COVID-19 illness. Assessment will be based on pregnancy test results, participant-reported symptomology, vital sign measurements, and physical examination findings. (Note: Sentinel participants will be required to remain at the study site for approximately 4 hours after study vaccination for observation. All other participants will be required to remain at the study site for approximately 60 minutes after study vaccination for observation.)

e. WOCBP only: A serum pregnancy test will be performed at Screening. A urine pregnancy test by dipstick will be performed prior to study vaccination. Negative confirmation is required prior to study vaccine administration.

f. Clinical SARS-CoV-2 serology testing will be performed at Screening and on D1 to confirm the serostatus of the participant and on D85 and D180 for detection of SARS-CoV 2 infection during the study. On D1, the serology sample should be collected before study vaccine administration. At baseline, D85, and D180 the serology analysis will include N protein to monitor for undetected SARS-CoV-2 infections. Binding IgG and neutralization will only be obtained at Day 85 and D180 in participants who did not receive a licensed or authorized COVID-19 vaccine after Day 29.

g. SARS-CoV-2 nasopharyngeal or mid-turbinate swab for RT-PCR diagnostic testing will be performed at Screening for eligibility and Day 1 for analysis (result not required for eligibility). The screening sample for RT-PCR testing must be obtained and tested within the 7 days before Day1. Additional swabs may be taken at any visit (or between visits) as clinically indicated according to institutional practice.

h. A complete physical examination including height and weight will be performed at Screening. Symptom-directed physical examinations will be performed as clinically indicated at subsequent visits.

i. Vital sign measurements (temperature, pulse rate, oxygen saturation by pulse oximetry, respiration rate, and blood pressure) should be collected before and after study vaccination on D1. Vital sign measurements should also be performed before any scheduled blood collection. Participants who are febrile (temperature ≥38.0°C or ≥100.4°F) before study vaccination on D1 should be rescheduled for study vaccination within the relevant window period of Screening.

j. Clinical safety laboratory testing will include hematology and serum chemistry. Screening laboratory tests may be repeated once for enrollment requirements. HIV 1/2, HB surface antigen, and anti-HCV testing will be performed at Screening only. Unscheduled visit may occur for the evaluation and follow-up of any AE. At unscheduled visits, clinical safety laboratory testing will be done as per investigator decision.

k. Blood draws for immunogenicity assessments (binding IgG and neutralization) after D29 will only be obtained from participants who have not yet received a COVID-19 booster vaccination with an authorized or licensed product.

l. Participants will be instructed to inform the investigator in the event of a positive SARS-CoV-2 diagnostic test. In this case, he/she will be invited to perform an unscheduled visit on site for COVID-19 evaluation according to the definitions provided in Section 6.6. All effort should be made by the investigator to ensure the disease assessment is performed in a timely manner versus the test results.

m. Solicited local and systemic AEs will be collected during the 7 days after study vaccination (Days 1 to 7) via eDiaries. Unsolicited AEs will be recorded for 28 days after study vaccination. SAEs, MAAEs, and AESIs will be collected for the duration of the study.

13.2 Appendix 2: Contraceptive Guidance and Pregnancy Information

Definitions:

Woman of Childbearing Potential

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

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

Contraception Guidance:

This contraception guidance is applicable to WOCBP in a heterosexual relationship (ie, this guidance does do not apply to participants in a same-sex relationship).

True abstinence is 100% of time no sexual intercourse (male's penis enters the female's vagina). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception).

Acceptable forms of primary contraception include monogamous relationship with a vasectomized partner who has been vasectomized for 180 days or more prior to the participant's study vaccination, intrauterine devices, birth control pills, tubal ligation, and injectable/implantable/insertable hormonal birth control products.

WOCBP must use at least 1 highly effective form of contraception for at least 30 days prior to study vaccination to 3 months after study vaccination.

Collection of Pregnancy Information from Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the PPD paper pregnancy report form and faxed to the same fax number as may be used for backup SAE reports within 24 hours after site personnel learn of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to the sponsor as described in Section 6.1.1.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

13.3 Appendix 3: Bayesian Logistic Regression Model

A Bayesian logistic regression model will be used to assess Grade 3 solicited AEs (Section 6.1.1.1.1) in an investigational group. The Bayesian logistic regression model is described by the following equation:

$$\text{logit}(p(d)) = (\alpha_1 + \beta_1 * \log(d/d^*)) + \beta_2 \text{ (indicator of OA)}$$

where

- p(d) represents the probability of having a Grade 3 event at dose d,
- logit(p) = ln(p/(1-p)),
- d* = 12 µg is the reference dose,
- α is an intercept parameter, reflecting the expected logit value at the 12 µg reference dose level,
- β_1 is a dose effect,
- β_2 is an age group effect.

The prior for α_1 and $\ln(\beta_1)$ is a mixture of 2 bivariate normal distributions:

1. 80% weight for $\alpha_1 \approx$ normal (mean=-0.8473, var=1) and $\ln(\beta_1) \approx$ normal (mean=0.2060, var=1), reflecting historical data from CVnCoV (ie, a rate of 30% at 12 µg, and 10% at 4 µg).
2. 20% weight for $\alpha_1 \approx$ normal (mean=-0.4055, var=1) and $\ln(\beta_1) \approx$ normal (mean=0.3678, var=1), reflecting an intolerable dose (ie, a rate of 40% at 12 µg and 12% at 4 µg).

The prior β_2 is half normal (mean=0, variance=0.25, $\beta_2<0$ to reflect lower reactogenicity in older age group [OA]).

The covariance between priors is assumed to be zero.

A 50% posterior probability that the rate at the next dose is greater than 30% will be used as a guide for the SRT recommendation on dose expansion and escalation. This will be applied

by dose and age group. Probabilities derived from the Bayesian model should be interpreted with caution when there is a low number of participants in a particular dose and age group.

Hypothetical scenarios that illustrate posterior probability based on combined younger age group and older age group data is presented in Table 13-2.

Table 13-2 Hypothetical Data Scenarios Illustrating Posterior Probabilities

Scenario	Dose	#Events	#Participants	CD – P(OD)	Next Dose	ND – P(TD)	ND – P(OD)
1	2	0	30	-	-	-	-
	4	0	30	0	8	0.946	0.054
	8	0	30	0	12	0.978	0.022
	12	0	30	0	16	0.997	0.003
	16	0	30	0	20	1.000	0.000
	20	0	30	0	NA		
2	2	0	30	-	-	-	-
	4	4	30	0.050	8	0.764	0.236
	8	6	30	0.071	12	0.563	0.437
	12	8	30	0.324	16	0.355	**0.645***
	16	15	30	0.973	20	0.006	**0.994***
	20	21	30	1.000	NA		

*This scenario, ND – P(OD) >0.5, would require SRT judgment to recommend proceeding with the current dose expansion and escalate to the next dose level.
Abbreviations: CD = current dose; NA = not applicable; ND = next dose; P(TD) = probability of tolerable dose; P(OD) = probability of overdose.
In this evaluation, the age effect was not considered in the model.
When fitting the model on more than 15 younger adult participants, 0 events (#events) are replaced by 1 event (ie, assume 1 event in the younger adult group); this is done to prevent results from being overinfluenced by rates of events (=0%) being on the boundary of the parameter space.

13.4 Appendix 4: Potential Immune-mediated Diseases

Potential immune-mediated diseases are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. Adverse events that need to be recorded and reported as pIMDs include those listed in Table 13-3.

However, the investigator will exercise their medical and scientific judgment in deciding whether other diseases have an autoimmune origin (that is pathophysiologically involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

When there is enough evidence to make any of the diagnoses mentioned in Table 13-3, the AE must be reported as a pIMD. Symptoms, signs, or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire will be available to investigators.

Once a pIMD is diagnosed (serious or nonserious) in a study participant, the investigator (or designate) must complete, date, and sign an electronic Expedited Adverse Events Report.

Table 13-3 List of Potential Immune-Mediated Diseases

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura

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

Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn’s disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis

Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (eg, 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: • Acute necrotizing myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis

Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (eg, Optic neuritis) • Idiopathic nerve palsies/paresis (eg, Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (eg, multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis

	• Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis)

	• Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
Goodpasture syndrome	• Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"
Immune-mediated enhancement of disease	• Includes vaccine-associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-associated enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)"
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome

Susac's syndrome	

13.5 Appendix 5: Tables for Laboratory Abnormalities

Any clinically relevant laboratory results should be reported as an AE using the FDA toxicity grading tables (excerpt provided in Table 13-4). Per the FDA tables, the laboratory values provided in Table 13-4 serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate, and laboratory results within institutional normal ranges will not be considered AEs.

Table 13-4 Toxicity Grading for Serum Laboratory Abnormalities

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hematology (Whole Blood)				
Hemoglobin (g/dL) - Female	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (g/dL) – Female Change from Baseline Value	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (g/dL) - Male	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (g/dL) - Male Change from Baseline Value	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Platelets Decrease (cell/mm^3)	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
WBC Increase (cell/mm^3)	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC Decrease (cell/mm^3)	2500 – 3500	1500 – 2499	1000 – 1499	<1000
Lymphocytes Decrease (cell/mm^3)	750 – 1000	500 – 749	250 – 499	<250
Neutrophils Decrease (cell/mm^3)	1500 – 2000	1000 – 1499	500 – 999	<500
Eosinophils (cell/mm^3)	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Biochemistry (Serum)				
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
ALT (increase by factor)	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10.0 × ULN
AST (increase by factor)	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10.0 × ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51-1.75 × ULN	> 1.75 × ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN
BUN (mg/dL)	23 – 26	27 – 31	>31	Requires dialysis
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of the normal range; WBC = white blood cells.
Source: DHHS 2007

13.6 Appendix 6: Protocol Amendment History

The document history table for this protocol and the Protocol Amendment Summary of Changes Table for the current Amendment 2 is located directly before the Protocol Synopsis.

A description of Amendment 1 is presented in this appendix.

Amendment 1, 20 Apr 2022

Rationale for Amendment 1:

The main purposes of Amendment 1 are to address feedback from FDA and to correct omissions and minor errors noted in the original protocol.

The summary of changes table provided here describes the important changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. The synopsis of Amendment 1 has been modified, as needed, to correspond to changes in the body of the protocol. Minor editorial and grammatical corrections were also made.

Throughout the document, the protocol date and version were updated to reflect Amendment 1 and the title page was updated to reflect the protocol history.

Summary of Important Changes from the Original Protocol to Amendment 1:

Section Number and Name	Description of Change	Brief Rationale
Title page, Protocol Approval – Sponsor Signatory page, page headers	The abbreviated title "CV2 SARS-COV2-002 BST" was added.	To provide a more informative protocol number.
Section 2 (Study Objectives and Endpoints, Table 2-1) Section 5.9 (Study Holding Rules, Table 5-2)) Section 6.1.1.1.1 (Adverse Events) Section 6.1.1.5 (eDiary) Section 13.1 (Appendix 1: Schedule of Events)	The description of the period of collection for solicited AEs was revised to read "…within the 7-day postvaccination period (Days 1 to 7)."	To correct a typographical error. and to provide further clarification regarding the follow-up period.
Section 3.1 (Study Design) Section 3.2 (Rationale for Study Design) Section 7.8 (Safety Review Team)	Text inserted to clarify that the SRT will review safety data from Days 1 to 8 (including Day 8 laboratory data).	To provide clarification regarding the safety data that will be reviewed by the SRT. This is consistent with the SRT Charter.

Section Number and Name	Description of Change	Brief Rationale
Section 5.9 (Study Holding Rules, Table 5-2)	Rule 1f was revised to read "any same or similar Grade 3 related unsolicited adverse events, including but not limited to the identical MedDRA high-level term".	To enhance safe conduct of the study and to address an FDA comment.
Section 6.1.1.2.1 (Assessment of Severity; Table 6-1)	For Temperature, Intensity Grade 3, the criterion now reads >102.0°F, rather than >102.1°F.	To correct a rounding error and to address an FDA comment.
Section 6.1.1.3.1 (Reporting Serious Adverse Events and Adverse Events of Special Interest)	Added the following 1-sentence paragraph: If the EDC is unavailable and a faxed form is used to report an SAE or AESI, the site should update the EDC with exactly the same information reported on paper (by fax) as soon as possible after the EDC becomes available again.	To clarify that the EDC must always be updated with SAE or AESI data as soon as possible after transmitting the same data by fax.
Section 6.2 (Pregnancy Reporting) Section 13.2 (Appendix 2: Contraceptive Guidance and Pregnancy Information)	Changed the heading name and modified the text to state that pregnancies are to be reported using paper forms faxed to the same fax number as may be used for backup SAE reports.	To clarify procedures for reporting detected pregnancies.
Section 13.1 (Appendix 1: Schedule of Events, Table 13-1)	Added marks to indicate that AEs and concomitant medications/vaccinations are collected at an ET visit.	To correct an omission and to address FDA comment.