CLINICAL STUDY PROTOCOL

A Phase 1, Open-label, Safety and Immunogenicity Study of a Booster Dose of the Investigational CV0501 mRNA COVID-19 Vaccine in Adults at Least 18 Years Old

PROTOCOL 218595 (CV2 SARS-COV2-012 BST)

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CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by GSK Biologicals SA. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the express written consent of GSK Biologicals SA.

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 and Immunogenicity Study of a Booster Dose of the Investigational CV0501 mRNA COVID-19 Vaccine in Adults at Least 18 Years Old
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Protocol Date and Version:	26 Jul 2022; Amendment 2
IND Number:	28462
EudraCT Number:	2022-001293-58

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Signature

26 Jul 2022

Date

Declaration of Investigator

I have read and understood all sections of the protocol titled "A Phase 1, Open-label, Safety and Immunogenicity Study of a Booster Dose of the Investigational CV0501 mRNA COVID-19 Vaccine in Adults at Least 18 Years Old" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 2, dated 26 Jul 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

Table of Contents

Table of Contents 5
List of Tables 9
List of Figures 9
List of Abbreviations and Definitions 10
Protocol Amendment Summary of Changes 13
Protocol Synopsis 15
1 Introduction 24
1.1 Background Information 24
1.2 Risk:Benefit Considerations 26
2 Study Objectives and Endpoints 29
3 Investigational Plan – Study Design 31
3.1 Part A Study Design 32
3.1.1 Part A Dose Escalation Plan 33
3.1.2 Part A Study Schematic 34
3.2 Part B Study Design 36
3.3 Scientific Rationale for Study Design 36
3.3.1 Starting Dose 37
3.3.2 Dose Escalation 38
3.3.3 Maximum Planned Dose 38
3.3.4 Low Dose Evaluation 39
4 Participant Selection and Withdrawal Criteria 40
4.1 Selection of Study Participants 40
4.1.1 Inclusion Criteria 40
4.1.2 Exclusion Criteria 41
4.2 Discontinuation From Study Intervention and/or Withdrawal From the Study 43
4.2.1 Lost to Follow-Up 44
4.2.2 Replacements 45

5 Study Vaccines 46
5.1 Method of Assigning Participants to Study Vaccine Groups 46
5.2 Study Vaccine Administration 46
5.3 Identity of Investigational Product 47
5.4 Management of Clinical Supplies 48
5.4.1 Investigational Product Packaging and Storage 48
5.4.2 Investigational Product Accountability 48
5.4.3 Other Supplies 49
5.5 Overdose Management 49
5.6 Blinding 50
5.7 Compliance With Study Vaccine 50
5.8 Prior, Concomitant, and Rescue Therapies 50
5.8.1 Prior and Concomitant Therapy 50
5.8.2 Allowed Concomitant Therapy 51
5.8.3 Rescue Medicine 51
5.9 Study Holding Rules 51
6 Study Assessments and Procedures 54
6.1 Safety Assessments 54
6.1.1 Adverse Events 55
6.1.1.1 Definitions 55
6.1.1.1.1 Adverse Events 55
6.1.1.1.2 Serious Adverse Events 56
6.1.1.1.3 Suspected Unexpected Serious Adverse Reactions 56
6.1.1.1.4 Adverse Events of Special Interest 56
6.1.1.2 Eliciting and Documenting Adverse Events 57
6.1.1.2.1 Assessment of Intensity 58
6.1.1.2.2 Assessment of Causality 60
6.1.1.3 Reporting Adverse Events 61
6.1.1.3.1 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 61
6.1.1.3.2 Reporting Suspected Unexpected Serious Adverse Reactions 62

6.1.1.4 Follow-Up of Participants Reporting Adverse Events 62
6.1.1.5 eDiary 63
6.1.2 SARS-CoV-2 Infection and COVID-19 Assessment and Definitions 63
6.1.3 Myocarditis and Pericarditis Assessment and Definitions 65
6.1.3.1 Surveillance for Asymptomatic Myocarditis and Pericarditis 66
6.1.4 Clinical Safety Laboratory Assessments 67
6.1.5 Physical Examinations 68
6.1.6 Vital Signs 68
6.2 Pregnancy Reporting 69
6.3 Assessment of Immune Responses 69
6.3.1 Assessment of Humoral Immune Responses 70
6.3.2 Assessment of Cellular Immune Responses 70
6.4 Genetics 70
7 Statistical Considerations 71
7.1 Statistical Hypothesis 71
7.2 Sample Size Determination 71
7.3 Analysis Sets 71
7.4 Description of Subgroups to Be Analyzed 72
7.5 Statistical Analysis Methodology 72
7.5.1 General Considerations 72
7.5.2 Analysis of the Primary Safety Endpoints 72
7.5.3 Analysis of Secondary Immunogenicity Endpoints 73
7.5.4 Analyses of Exploratory Immunogenicity Endpoints 73
7.5.5 Safety Analyses 73
7.5.6 Other Analyses 73
7.6 Handling of Missing Data 74
7.7 Interim Analyses 74
8 Data Quality Assurance 75
8.1 Data Management 75
9 Ethics 76

9.1 Independent Ethics Committee or Institutional Review Board 76
9.2 Ethical Conduct of the Study 76
9.3 Participant Information and eConsent 77
10 Investigator's Obligations 78
10.1 Confidentiality 78
10.2 Data Protection 78
10.3 Financial Disclosure and Obligations 78
10.4 Investigator Documentation 79
10.5 Study Conduct 79
10.6 Adverse Events and Study Report Requirements 79
10.7 Investigator's Final Report 79
10.8 Records Retention 80
10.9 Publications and Results Disclosures 80
11 Study Management 81
11.1 Safety Review Team 81
11.2 Monitoring 81
11.2.1 Monitoring of the Study 81
11.2.2 Inspection of Records 82
11.3 Management of Protocol Amendments and Deviations 82
11.3.1 Modification of the Protocol 82
11.3.2 Protocol Deviations 82
11.4 Study Termination 83
11.5 Final Report 83
12 References 85
13 Appendices 88
13.1 Appendix 1: Schedule of Events 88
13.2 Appendix 2: Contraceptive Guidance and Pregnancy Information 92
13.3 Appendix 3: Bayesian Logistic Regression Model 95
13.4 Appendix 4: Potential Immune-mediated Diseases 97

13.5 Appendix 5: Grading for Laboratory Abnormalities 105
13.6 Appendix 6: Protocol Amendment History..... 107

List of Tables

Table 2-1 Study Objectives and Endpoints..... 29
Table 3-1 Planned Cohorts, Dose Levels, Groups, and Sample Sizes for Part A 32
Table 3-2 Dosing Scenarios for Participants Enrolled in Cohorts 4 and 5 33
Table 3-3 Planned Cohorts, Dose Levels, Groups, and Sample Sizes for Part B 36
Table 5-1 Investigational Product Information..... 47
Table 5-2 Study Holding Rules 52
Table 6-1 Intensity Scales for Solicited Symptoms..... 59
Table 13-1 Schedule of Events..... 89
Table 13-2 Hypothetical Data Scenarios for Determining Posterior Probabilities 96
Table 13-3 List of Potential Immune-Mediated Diseases..... 97
Table 13-4 Toxicity Grading for Serum Laboratory Abnormalities 106

List of Figures

Figure 3-1 Part A Study Schematic 35
Figure 3-2 Part B Study Schematic..... 36

List of Abbreviations and Definitions

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
CCI	[redacted]
COVID-19	coronavirus disease caused by SARS-CoV-2
CV0501	an investigational, monovalent, nucleoside-modified, mRNA COVID-19 vaccine targeting the Omicron variant of SARS-CoV-2
CCI	[redacted]
D	Day
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
ET	early termination
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
FTiH	first-time-in human

Abbreviation	Definition
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
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
N protein	nucleocapsid protein
PaO2/FiO2	partial pressure of oxygen/fraction of inspired oxygen
PBMC	peripheral blood mononuclear cell
pIMD	potential immune-mediated disease
PPI	per protocol immunogenicity
SAP	statistical analysis plan
RT-PCR	reverse transcription polymerase chain reaction
S protein	spike protein

Abbreviation	Definition
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOE	schedule of events
SOP	standard operating procedure
CCI	[redacted]
SpO2	blood oxygen saturation
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
VRBPAC	Vaccines and Related Biological Products Advisory Committee
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	26 Jul 2022
Amendment 1	23 Jun 2022
Original Protocol	20 Apr 2022

Amendment 2, 26 Jul 2022: Current Amendment

Rationale for Amendment 2:

The rationale for Amendment 2 is to add a 12-lead ECG examination at screening, to facilitate a comprehensive cardiac safety assessment in the event of a participant's abnormal Day 8 ECG examination.

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 3.1.1 (Part A Dose Escalation Plan) Section 11.1 (Safety Review Team)	Removed references to an SRT charter	The SRT charter has been retired. As per GSK process, the content contained within GSK SRT Charters is now documented in the GSK SOP, VQD-SOP-069378 Benefit-Risk Assessment at the Safety Review Team.
Section 6.1.3.1 (Surveillance for Asymptomatic Myocarditis and Pericarditis) Section 13.1 (Appendix 1: Schedule of Events)	Added a 12-lead ECG baseline examination at screening	In the event of a participant's abnormal Day 8 ECG examination, the screening ECG provides a baseline for comparison.

Section Number and Name	Description of Change	Brief Rationale
Section 6.1.3 (Myocarditis and Pericarditis Assessment and Definitions) Section 6.1.3.1 (Surveillance for Asymptomatic Myocarditis and Pericarditis)	Revised "PR-segment inversion" to "PR-segment depression"	Revised to provide correct terminology: PR-segment depression may be indicative of pericarditis.

Protocol Synopsis

Protocol Number: 218595 (CV2 SARS-CV0501-012 BST)

Title: A Phase 1, Open-label, Safety and Immunogenicity Study of a Booster Dose of the Investigational CV0501 mRNA COVID-19 Vaccine in Adults at Least 18 Years Old

Short Title: Phase 1 Safety and Immunogenicity Study of a Booster Dose of CV0501 mRNA COVID-19 Vaccine in Adults

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

Study Phase: 1

Proposed Indication: Prevention of COVID-19

Rationale: Due to the ongoing COVID-19 pandemic and the need for vaccines to provide protection against COVID-19 caused by SARS-CoV-2 variants of concern, GSK and CCI [redacted] are collaborating to develop the CV0501 mRNA vaccine. This is a Phase 1 FTiH study designed to evaluate the safety and immunogenicity of the GSK CCI [redacted] CV0501 mRNA vaccine administered as a booster vaccination in previously vaccinated adults. The proposed study will guide selection of the optimal dose to be evaluated in Phase 2.

Objectives and Endpoints:

Objectives	Endpoints
Primary – Safety and Tolerability	
To evaluate the safety and tolerability of CV0501 at each dose level	• Percentage of participants with each solicited local and systemic AE during 7 days after vaccination (ie, the day of study vaccination and 6 subsequent days, Days 1 through 7) • Percentage of participants with abnormal laboratory findings for 8 days after study vaccination • Percentage of participants with unsolicited AEs for 28 days after study vaccination • Percentage of participants with MAAEs, SAEs, and AESIs from study vaccination through the end of the study (180 days after the study vaccine administration), each summarized separately
Secondary – Immunogenicity	
To evaluate neutralizing Ab titers against SARS-CoV-2 WT, Omicron, and Delta variants following CV0501 booster vaccination in adult participants	• GMTs of neutralizing Ab titers against pseudovirus bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection timepoint • GMI from baseline of neutralizing Ab titers against pseudovirus bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection time point
To describe seroresponse to CV0501 based on neutralizing Ab titers against pseudoviruses bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants	• Seroresponse rate 28 days after the booster dose (Day 29), based on neutralizing Ab titers against pseudoviruses bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection timepoint, with seroresponse defined as postboost titers ≥ 4× preboost titers.

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

Diagnosis and Main Criteria for Inclusion and Exclusion: The study will enroll healthy male and female adults, at least 18 years old, who have received at least 2 doses of mRNA COVID-19 vaccine[redacted] with the last dose received at least 6 months prior to screening. Participants must be negative for SARS-CoV-2 infection (by RT-PCR test) at screening. Participants who have had close contact with anyone who had a confirmed SARS-CoV-2 infection within 2 weeks before study vaccination will be excluded from study participation.

Study Design:

This open-label, dose escalation, FTiH Phase 1 study will evaluate the safety (including reactogenicity) and immunogenicity of a single booster dose of CV0501 vaccine in adults who have previously received at least 2 doses of an mRNA COVID-19 vaccine. Approximately 180 participants will be enrolled. The study will comprise two parts (Part A and Part B).

The study duration per participant will be approximately 194 days from start of screening through EOS, including approximately 14 days for screening and approximately 180 days (6 months) for Day 1 vaccination and follow-up. There will be 6 protocol-scheduled visits: on Day 1 (vaccination day) and on Days 8, 15, 29, 91 and 181. In addition, there will be one protocol-scheduled telephone contact on Day 4 to query participants about solicited and unsolicited AEs occurring after study vaccination.

[redacted]

Participants will be monitored for potential COVID-19 illness from Day 1 through the EOS (Day 181). Participants will be asked to contact the site if they experience any symptoms of COVID-19. An unscheduled visit may be performed to evaluate the potential infection. Alternatively, an investigator may utilize subject medical records from non-study care medical providers to verify whether a participant was infected with SARS-CoV-2. An

additional unscheduled COVID-19 convalescent visit may be performed for all participants with confirmed COVID-19.

Participants will also be required to document all AE symptoms and contact the site if necessary. An unscheduled visit may also be performed if an AE requires further evaluation.

Safety data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor to promptly identify and flag any event that potentially could trigger a stopping rule. If a stopping rule is triggered, study intervention administration and enrollment will pause and the SRT will review available safety data from all vaccinated participants. Participants who have already received vaccine will continue to attend follow-up visits as specified in the schedule of events.

Part A:

Participants in Cohorts 1 to 5 will be enrolled in a staggered manner to 1 of 5 cohorts with planned dose escalation of CV0501 from 12 µg up to 200 µg. Each cohort of Part A will evaluate a single-dose level of CV0501 vaccine and will include 2 age groups (younger adults, ≥ 18 to < 65 years old, and older adults, ≥ 65 years old). The dose levels for the groups in Cohorts 1-3 are fixed. The dose levels for the Cohorts 4 and 5 will be as recommended by the SRT, based on their review of all available safety data and dosing scenarios.

Planned Cohorts, Dose Levels, Groups, and Sample Sizes for Part A

Cohort	Vaccine	Dose Level (µg)	Group A Younger Adults ≥18 to <65 Years Old (n range)	Group B Older Adults ≥65 Years Old (n range)	Total Cohort Sample Size
1	CV0501	12	1a (min 10; max 20)	1b (min 10; max 20)	30
2		25	2a (min 10; max 20)	2b (min 10; max 20)	30
3		50	3a (min 10; max 20)	3b (min 10; max 20)	30
4		75 or 100*	4a (min 10; max 20)	4b (min 10; max 20)	30
5		100, 150, or 200*	5a (min 10; max 20)	5b (min 10; max 20)	30

* Depending on the reactogenicity/safety findings from groups in Cohorts 1-3, the SRT may recommend 1 of 3 prespecified dosing scenarios comprising these dose levels for groups in Cohorts 4 and 5. The dose level recommendations will be made independently for Groups A (younger participants) and B (older participants).

The recruitment target will be a total of 30 participants per cohort in Cohorts 1 to 5. The 30 participants will be distributed between the younger and older age groups. A minimum of 10 participants per age group will be enrolled. A maximum of 20 participants may be enrolled in an individual age group. CCI [redacted]

Enrollment will be staggered, beginning with Group 1a (12 µg, younger adults). Initiation of enrollment in Group 1b (12 µg, older adults) will depend on SRT review of safety data up to Day 8 from a minimum of 10 participants in Group 1a.

For both younger and older age groups, initiation of enrollment in the subsequent group at the next dose level for Cohorts 2-5 will depend on SRT review of safety data up to Day 8 from a minimum of 10 participants, from the previous dose level in the same age group. The dose levels for the groups in Cohorts 1-3 are fixed. For each of the groups in Cohorts 4 and 5, the SRT may recommend a dose specified by 1 of the 3 dosing scenarios in the dosing scenario table (below), based on their review of all available safety data. The SRT will use the same approach, independently, to select the dose levels for older participants (Groups 4b and 5b) and younger participants (Groups 4a and 5a).

Dosing Scenarios for Participants Enrolled in Cohorts 4 and 5

Dosing Scenario	Group 4a OR 4b	Group 5a OR 5b
#1	75 µg	100 µg
#2	100 µg	150 µg
#3	100 µg	200 µg

While the SRT reviews safety data, enrollment in the same group will continue until the cohort is full. The SRT recommendation for each group could be to escalate to the next dose level or to stop the enrollment at the current dose.

At each SRT meeting, a Bayesian logistic regression model will be used to predict unacceptable reactogenicity at the current or next dose level. A lower than 50% posterior probability that the percentage is above the maximum tolerable rate will be favorable to progression to the next higher dose. Based on the historical Phase 1 reactogenicity data from CCI [redacted], the maximum tolerable rate for Grade 3 solicited adverse events has been set to 30%. The SRT may recommend dropping groups 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.

Part B:

Part B, designed to comprise 2 single age group cohorts, will start based on the first interim analysis of safety and immunogenicity, provided that the SRT assesses the 12 µg dose to be immunogenic and safe. The SRT may recommend dropping Cohorts 6 and 7 (Groups 6a and 7a) based on immunogenicity data from the groups that received the 12 µg dose level. If the SRT determines that enrollment in Cohorts 6 and 7 may proceed, enrollment may proceed in parallel according to the table below.

Planned Cohorts, Dose Levels, Groups, and Sample Sizes for Part B

Cohort	Vaccine	Dose Level (µg)	Group A ≥18 to <65 Years Old	Total Cohort Sample Size
6	CV0501	3	6a	15
7		6	7a	15

Study Duration:

The study duration per participant will be approximately 194 days from start of screening through EOS, including approximately 14 days for screening and approximately 180 days (6 months) for Day 1 vaccination and follow-up.

Safety Assessments:

Safety will be assessed through the collection and evaluation of solicited AEs (for 7 days, the day of vaccination and 6 subsequent days); unsolicited AEs (for 28 days after study vaccination); and MAAEs, SAEs, and AESIs for the duration of the study. Local solicited AEs will include injection site pain, redness, and swelling and localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the vaccination arm (lymphadenopathy). Systemic solicited AEs will include fever, fatigue, headache, chills, myalgia, and arthralgia. AESIs will include virologically confirmed COVID-19 disease, pIMDs, anaphylaxis or severe hypersensitivity within 24 hours after study vaccine administration, myocarditis, and pericarditis. Safety will also be assessed based on physical examinations, vital sign measurements, and clinical safety laboratory assessments (scheduled only at screening, Day 1, and Day 8).

Assessment of Immune Responses:

Blood samples will be collected to evaluate vaccine-induced neutralizing Ab levels, binding IgG Ab levels, and T-cell immune response.

For assessment of humoral immune response, neutralizing Ab levels against pseudotyped virus displaying S protein from SARS-CoV-2 WT, Omicron, Delta, and potentially other

relevant variants will be measured. Binding IgG Ab levels against SARS-CoV-2 WT S protein and SARS-CoV-2 S antigens from other variants will be measured.

For assessment of cellular immune response, [redacted]

Investigational Product, Dosage, and Route of Administration:

Study vaccine will be administered on Day 1 as a single IM injection in the deltoid area, preferably in the nondominant arm. The volume to be administered will vary by dose level over a potential range of 0.3 mL to 0.7 mL.

The mRNA in the IP will encode the S protein of the Omicron SARS-CoV-2 variant.

Sample Size:

Approximately 180 healthy adult participants will be enrolled in the study as described in Study Design, above.

Statistical Methods:

All analyses will be performed by treatment group, combining the younger and older adult participants together, unless specified otherwise. 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). For continuous immunogenicity variables, confidence interval and interquartile range will also be provided.

For all safety endpoints, descriptive summary statistics will be provided for the Safety Set, which includes all participants vaccinated under this protocol.

For the key immunogenicity endpoints, seroresponse rate with 95% CI, GMT of specific Ab with corresponding 95% CI at each timepoint and GMI of specific Ab with corresponding 95% CI at each postbaseline timepoint over prevaccination baseline will be provided by group. The GMT, the GMI, and their 95% CIs in all cohorts will be analyzed using an

ANCOVA with treatment and age group as fixed factors and prevaccination baseline value as a covariable.

Interim Analyses:

There are 2 planned interim analyses of safety and immunogenicity data. The first interim analysis will be performed after all participants in Cohorts 1, 2, and 3 have completed the Day 15 study visit. The second interim analysis will be performed after all participants in Cohorts 4 and 5 have completed the Day 15 study visit.

1 Introduction

1.1 Background Information

The COVID-19 pandemic caused by SARS-CoV-2 virus was declared by the WHO on 11 Mar 2020 (WHO 2020). As of 19 Jan 2022, more than 332 million cases have been reported worldwide, leading to more than 5.5 million deaths (WHO 2022). To date, there are multiple licensed or conditionally approved vaccines available that rely on a variety of vaccine technologies. All currently available vaccines are based on antigens from the original Wuhan strain (D614; wild-type, hereafter referred to as "WT").

Half (50.3%) of the world population is fully vaccinated with any SARS-CoV-2 vaccine and among this group, 10.9% have received a booster or additional dose. Vaccination rates vary starkly by country and region: the proportion that was fully vaccinated in the US and Canada was 62.5% and 78.1%, respectively, versus 10.1% in Africa (Our World in Data 2022). Vaccine distribution is inequitable worldwide and the WHO currently prioritizes primary series vaccination for this reason, though only about 20% of all COVID-19 vaccines are used as booster doses (WHO 2021). Authorizing additional vaccines to only be used as booster doses could help thwart the spread of Omicron without diverting primary dose resources from populations in need.

Real world data from Israel and presented to the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) demonstrated that immunity to SARS-CoV-2 in adults vaccinated with 2 doses of the CCI [redacted] vaccine wanes over time across all age groups, is most pronounced among individuals in older adults, and that booster doses protect against severe COVID-19, including against the Delta variant (Alroy-Preis and Milo 2021). Based on these and other data, the VRBPAC voted unanimously to recommend that a booster dose of CCI [redacted] be administered at least 6 months after completion of the primary series in individuals 65 years of age and older (FDA 2021).

Several variants of concern have emerged, including Delta and more recently Omicron. The transmissibility of Omicron is estimated to be higher than Delta, and UK data have indicated that the risk of reinfection among those with a prior COVID-19 infection is 3-8 times higher from Omicron than Delta. (UK Health Security Agency 2021).

For the week ending 18 Dec 2021, the US CDC estimated that Omicron infections were 73.2% of all SARS-CoV-2 infections in the US, with Delta infections at 23.6% (CDC 2021b). For the week ending 27 Nov 2021, Omicron had not been detected in the US (MMWR 2021), and Delta was 99.7% of all SARS-CoV-2 infections.

Data published in MedRxiv preprint reports have indicated that mRNA vaccines encoding WT S protein are substantially less effective against Omicron than against Delta within the 1 to 3 months following the 2-dose primary vaccination series, and the durability of effectiveness over the next 3 to 6 months is also substantially less against Omicron than Delta (Andrews et al 2021; Buchan et al 2021; Hansen et al 2022; Tseng et al 2022). The same data appear to indicate a similar pattern of vaccine effectiveness against Omicron and Delta variants following a booster dose of mRNA vaccines encoding WT S protein.

With the surge in Omicron predominance worldwide, its greater transmissibility, and a higher risk of SARS-CoV-2 reinfection with Omicron, it is reasonable to anticipate an urgent need for booster shots to expand immunity against Omicron and additional future variants of concern.

CCI previously developed an mRNA vaccine CCI using the unmodified WT S protein mRNA sequence, for which vaccine safety and efficacy are being evaluated CCI. Interim results from the Phase 2b/3 trial of CCI showed vaccine efficacy of 48% against COVID-19 of all severities across all age groups and 15 different virus variants (including Delta, but before emergence of Omicron), with an acceptable vaccine safety profile (Kremsner 2021). 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 204/228 adjudicated cases (83 in the CCI group and 145 in the placebo group) to identify the variant causing the infection. Approximately 86% of sequenced cases were caused by either variants of concern (~51%) or variants of interest (~35%). Approximately 3% were attributable to the WT SARS-CoV-2 virus, while the remaining 11% were caused by less-investigated strains. Collectively, these results demonstrated the need for protection against emerging SARS-CoV-2 variants.

Separately, the [redacted] vaccine was tested (along with 6 other COVID-19 vaccines) as a single-dose booster after 2 doses of either [redacted] vaccines (Munro et al 2021). The [redacted] vaccine boosted immunity after both primary series, as judged by anti-S IgG and neutralizing assays, although to a lesser extent than boosting with either the [redacted] vaccines.

GSK and [redacted] are collaborating to develop CV0501, a modified-nucleotide mRNA vaccine based on the same LNP. platform as the [redacted] vaccine. The CV0501 mRNA encodes S protein from the Omicron variant and has been optimized to improve intracellular mRNA stability and translation for increased and extended protein expression, relative to unmodified S protein mRNA (Section 5.3).

The CV0501 vaccine will be intended to be administered as a single booster dose for active immunization to prevent COVID -19 in adults at least 18 years old who have previously received at least 2 doses of an mRNA COVID-19 vaccine. This Phase 1 clinical study is being initiated to evaluate the safety and immunogenicity of CV0501 as a booster vaccine over a range of dose levels in adults at least 18 years old.

1.2 Risk:Benefit Considerations

Detailed information about the known and expected risks of the CV0501 vaccine is provided in the current IB. Important potential risks for CV0501 vaccine are the following:

- Hypersensitivity reactions, including anaphylaxis
- Myocarditis
- Pericarditis
- Vaccine-associated disease enhancement (an important risk for all SARS-CoV-2 vaccines)

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

- All participants will remain under observation at the vaccination center for at least 60 minutes after vaccination.

- Individuals 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.

- Individuals at increased risk of myocarditis or pericarditis and individuals with history of myocarditis or pericarditis are excluded from the study enrollment. All participants will be educated on the symptoms of myocarditis and pericarditis and will receive guidance on contacting study personnel and seeking medical care if any of these symptoms occur. Any participants with suspected myocarditis or pericarditis within 4 weeks after study vaccination will be evaluated by a cardiologist for definitive diagnosis and management.

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

In addition, vasovagal syncope and other anxiety related reactions as a psychogenic response to the needle injection can occur following or even before any vaccination. All participants will therefore remain under observation at the vaccination center for at least 60 minutes after vaccination.

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 Phase 3.

Due to the lack of experience in human participants, there is currently not enough information available about the relationship between administration of the CV0501 mRNA investigational vaccine and AEs. Although there are no clinical data available on the use of CV0501 in humans, available clinical data from other mRNA vaccines using a similar modified mRNA platform CCI [redacted] and nonclinical

data using the unmodified mRNA [redacted] investigational vaccine guide the projection of expected AEs after vaccination. Based on this assessment, the anticipated AEs are expected to be manageable.

The CV0501 vaccine is currently in an early stage of clinical development. As a result, vaccine efficacy, immunogenicity, and safety have not been demonstrated in humans. Considering the measures planned to be taken to minimize risk to participants in this Phase 1 study, the potential risks associated with the investigational vaccine 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

Primary Objectives	Primary Endpoints
To evaluate the safety and tolerability of CV0501 at each dose level	• Percentage of participants with each solicited local and systemic AE during 7 days after vaccination (ie, the day of study vaccination and 6 subsequent days, Days 1 through 7) • Percentage of participants with each abnormal clinical safety laboratory finding for 8 days after study vaccination • Percentage of participants with unsolicited AEs for 28 days after study vaccination • Percentage of participants with MAAEs, AESIs and SAEs from study vaccination through the end of the study (for 180 days after the study vaccine administration), each summarized separately
Secondary Objectives	**Secondary Endpoints**
To evaluate neutralizing Ab titers against SARS-CoV-2 WT, Omicron, and Delta variants following CV0501 booster vaccination in adult participants	• GMTs of neutralizing Ab against pseudovirus bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection timepoint • GMI from baseline of neutralizing Ab titers against pseudovirus bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection time point
To describe seroresponse to CV0501 based on neutralizing Ab titers against pseudoviruses bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants	• Seroresponse rate 28 days after the booster dose (Day 29), based on neutralizing Ab titers against pseudoviruses bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection timepoint, with seroresponse defined as postboost titers $\geq 4\times$ preboost titers.
Tertiary Objectives	**Tertiary Endpoints:**
CCI [redacted]	

CCI

3 Investigational Plan – Study Design

This open-label, dose escalation FTiH Phase 1 study will evaluate the safety (including reactogenicity) and immunogenicity of a single booster dose of CV0501 vaccine in adults who have previously received at least 2 doses of an mRNA COVID-19 vaccine (Section 4.1.1). Approximately 180 participants will be enrolled. The study will comprise two parts (Part A and Part B).

The study duration per participant will be approximately 194 days from start of screening through EOS, including approximately 14 days for screening and approximately 180 days (6 months) for Day 1 vaccination and follow-up. There will be 6 protocol-scheduled visits: on Day 1 (vaccination day) and on Days 8, 15, 29, 91 and 181. In addition, there will be one protocol-scheduled telephone contact on Day 4 to query participants about solicited and unsolicited AEs occurring after study vaccination.

CCI

Participants will be monitored for potential COVID-19 illness from Day 1 through the EOS (Day 181). Participants will be asked to contact the site if they experience any symptoms of COVID-19 and will also be asked to report any positive SARS-CoV-2 diagnostic test.

Participants will also be required to document all AE symptoms and contact the site if necessary. An unscheduled visit may also be performed if an AE requires further evaluation.

Safety data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor to promptly identify and flag any event that potentially could trigger a stopping rule. If a stopping rule is triggered, study intervention administration and enrollment will pause and the SRT will review available safety data from all vaccinated participants. Participants who have already received vaccine will continue to attend follow-up visits as specified in the schedule of events (Table 13-1). There are 2 planned interim analyses of safety and immunogenicity data (Section 7.7).

3.1 Part A Study Design

Participants in Cohorts 1 to 5 will be enrolled in a staggered manner to 1 of 5 cohorts with planned dose escalation of CV0501 from 12 µg up to 200 µg. Each cohort of Part A will evaluate a single dose level of CV0501 vaccine and will include 2 age groups (younger adults, ≥ 18 to < 65 years old, and older adults, ≥ 65 years old), as indicated in Table 3-1. The dose levels for the groups in Cohorts 1-3 are fixed. The dose levels for the Cohorts 4 and 5 will be as recommended by the SRT, based on their review of all available safety data and dosing scenarios.

Table 3-1 Planned Cohorts, Dose Levels, Groups, and Sample Sizes for Part A

Cohort	Vaccine	Dose Level (µg)	Group A Younger Adults ≥18 to <65 Years Old (n range)	Group B Older Adults ≥65 Years Old (n range)	Total Cohort Sample Size
1	CV0501	12	1a (min 10; max 20)	1b (min 10; max 20)	30
2		25	2a (min 10; max 20)	2b (min 10; max 20)	30
3		50	3a (min 10; max 20)	3b (min 10; max 20)	30
4		75 or 100*	4a (min 10; max 20)	4b (min 10; max 20)	30
5		100, 150, or 200*	5a (min 10; max 20)	5b (min 10; max 20)	30

* Depending on the reactogenicity/safety findings from groups in Cohorts 1-3, the SRT may recommend 1 of 3 prespecified dosing scenarios comprising these dose levels for groups in Cohorts 4 and 5, as described in Section 3.1.1. The dose level recommendations will be made independently for Groups A (younger participants) and B (older participants).

The recruitment target will be a total of 30 participants per cohort in Cohorts 1 to 5. The 30 participants will be distributed between the younger and older age groups. A minimum of 10 participants per age group will be enrolled. A maximum of 20 participants may be enrolled in an individual age group. CCI [redacted]

3.1.1 Part A Dose Escalation Plan

Enrollment will be staggered, beginning with Group 1a (12 µg, younger adults). Initiation of enrollment in Group 1b (12 µg, older adults) will depend on SRT review of safety data up to Day 8 from a minimum of 10 participants in Group 1a (Figure 3-1, red arrow).

For both younger and older age groups, initiation of enrollment in the subsequent group at the next dose level for Cohorts 2-5 will depend on SRT review of safety data up to Day 8 from a minimum of 10 participants, from the previous dose level in the same age group (Figure 3-1, black arrows). The dose levels for the groups in Cohorts 1-3 are fixed. For each of the groups in Cohorts 4 and 5, the SRT may recommend a dose specified by 1 of the 3 dosing scenarios in Table 3-2, based on their review of all available safety data. The SRT will use the same approach, independently, to select the dose levels for older participants (Groups 4b and 5b) and younger participants (Groups 4a and 5a).

Table 3-2 Dosing Scenarios for Participants Enrolled in Cohorts 4 and 5

Dosing Scenario	Group 4a OR 4b	Group 5a OR 5b
#1	75 µg	100 µg
#2	100 µg	150 µg
#3	100 µg	200 µg

While the SRT reviews safety data, enrollment in the same group will continue until the cohort is full. The SRT recommendation for each group could be to escalate to the next dose level or to stop the enrollment at the current dose.

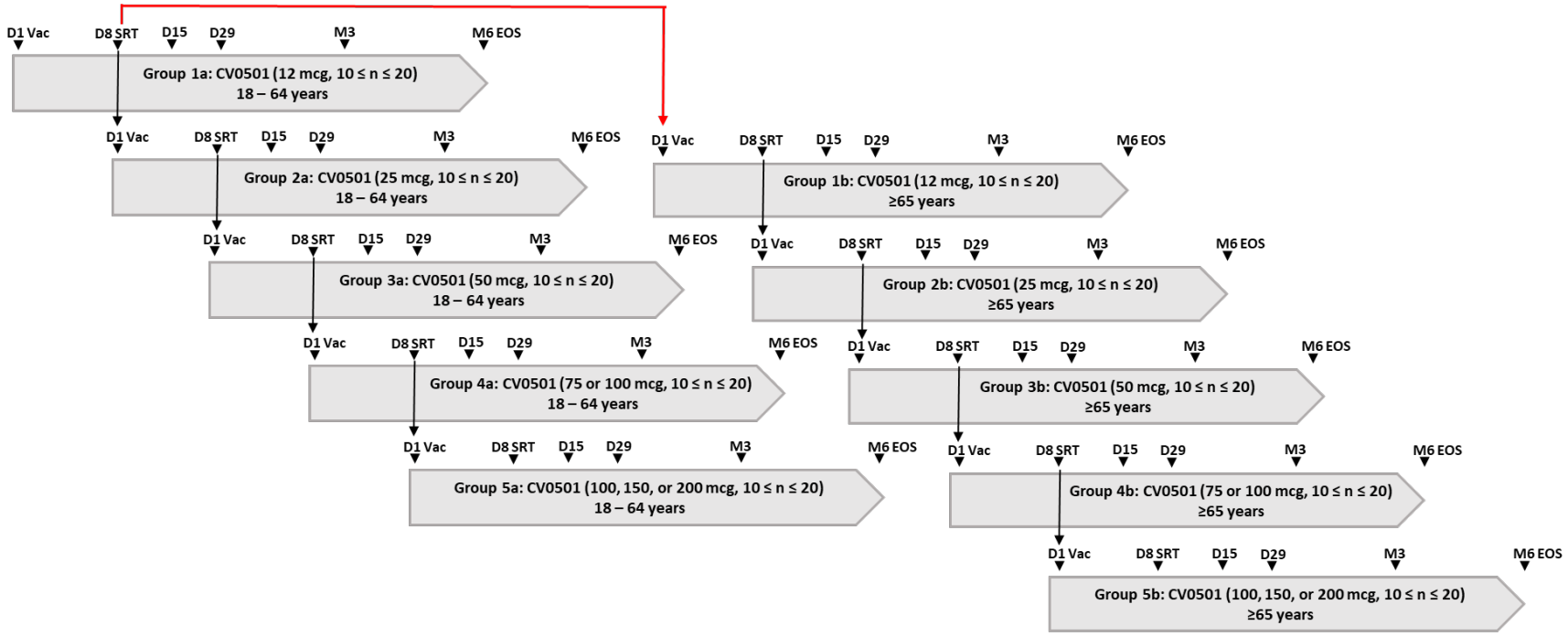
At each SRT meeting, a Bayesian logistic regression model (Section 13.3) will be used to predict unacceptable reactogenicity at the current or next dose level. A lower than 50% posterior probability that the percentage is above the maximum tolerable rate will be favorable to progression to the next higher dose. Based on the historical Phase 1 reactogenicity data from cci vaccines, the maximum tolerable rate for Grade 3 solicited adverse events has been set to 30%. The SRT may recommend dropping groups 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.

3.1.2 Part A Study Schematic

The study schematic of Part A is provided in Figure 3-1.

Figure 3-1 Part A Study Schematic



Note for Cohort 4 (Groups 4a and 4b) and Cohort 5 (Groups 5a and 5b): Depending on the reactogenicity/safety findings from groups in Cohorts 1-3, the SRT may prospectively recommend a dose of 75 µg or 100 µg for Groups 4a and 4b, and subsequently a dose of 100 µg, 150 µg or 200 µg for Groups 5a and 5b. The dose level recommendations will be made independently for Groups A (younger participants) and B (older participants).

3.2 Part B Study Design

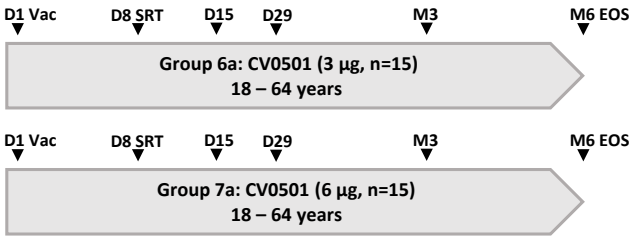
Part B, designed to comprise 2 single age group cohorts (≥18 to <65 years old), will start based on the first interim analysis of safety and immunogenicity (Section 7.7), provided that the SRT assesses the 12 µg dose to be immunogenic and safe. The SRT may recommend dropping Cohorts 6 and 7 (Groups 6a and 7a) based on immunogenicity data from the groups that received the 12 µg dose level. If the SRT determines that enrollment in Cohorts 6 and 7 may proceed, enrollment may proceed in parallel according to Table 3-3.

Table 3-3 Planned Cohorts, Dose Levels, Groups, and Sample Sizes for Part B

Cohort	Vaccine	Dose Level (µg)	Group A ≥18 to <65 Years Old	Total Cohort Sample Size
6	CV0501	3	6a	15
7		6	7a	15

The study schematic for Part B is provided in Figure 3-2. The SRT will review Day 8 safety data for all 15 participants in Groups 6a and 7a.

Figure 3-2 Part B Study Schematic



Note: Initiation of enrollment for Groups 6a and 7a will be dependent on SRT review of safety and immunogenicity data from the first interim analysis (after all participants in Cohorts 1, 2, and 3 have completed the Day 15 study visit).

3.3 Scientific Rationale for Study Design

There is currently a critical unmet medical need for vaccines to prevent COVID-19 disease caused by the Omicron variant (B.1.1.529) of SARS-CoV-2. The transmissibility of Omicron variant is estimated to be higher than Delta, and preliminary clinical data indicate that the risk of reinfection among those with a prior COVID-19 infection is 3-8 times higher from

Omicron than Delta. (UK Health Security Agency 2021). Although current FDA-authorized and licensed COVID-19 vaccines are highly effective, breakthrough cases occur. A total of 10,262 SARS-CoV-2 vaccine breakthrough infections had been reported from 46 US states and territories as of April 30, 2021 (CDC 2021c).

In partnership with CCI GlaxoSmithKline Biologicals SA (GSK) is developing a new CV0501 COVID-19 vaccine comprising modified-nucleotide mRNA that encodes the Omicron variant S protein formulated with lipid nanoparticles (LNPs).

This is a Phase 1 FTiH study designed to evaluate the safety, reactogenicity, and immunogenicity of the GSK-CCI CV0501 modified mRNA vaccine encoding the Omicron variant to prevent COVID-19. This study will evaluate the CV0501 vaccine as a booster vaccination in a healthy adult population of participants who have previously received at least 2 doses of an mRNA COVID-19 vaccine.

3.3.1 Starting Dose

The starting dose of CV0501 vaccine (12 µg) has been chosen based on a repeat-dose toxicity study of 10 µg or 20 µg doses of the CCI unmodified SARS-CoV-2 mRNA vaccine, CCI (Section 1.1). Please refer to the current IB for additional details on data from nonclinical toxicology studies support initiation of the starting dose.

Clinical safety data with CCI an investigational LNP mRNA-based vaccine encoding the SARS-CoV-2 Spike protein of the Wuhan ancestral isolate manufactured by CCI further support the starting dose of 12 µg for the present study. CCI consists of sequence-optimized, capped and polyadenylated, chemically unmodified mRNA. Vaccines containing modified mRNA, such as CV0501, are expected to have less reactogenicity than vaccines containing unmodified mRNA because modified mRNA does not engage endosomal and cytosolic pattern-recognition receptors and so provoke less inflammation. The reduced inflammation is expected to yield a more favorable safety profile.

Study CCI is an ongoing Phase 2b/3, randomized, observer-blinded, placebo-controlled, multicenter, clinical study evaluating the efficacy and safety of investigational CVnCoV vaccine in adults at least 18 years old. In the final analysis

with data cutoff date of 17 Jun 2021, 19,783 participants received at least 1 dose of 12 µg [redacted] and 19,746 participants at least 1 dose of placebo.

Based on data from the ongoing [redacted] trial, the reactogenicity profile is considered acceptable with most solicited AEs being Grade 1 or Grade 2. Any Grade 3 solicited AEs were transient, with a median duration of 1 day. Local reactions were more common in participants receiving [redacted] (84.8%) than in those receiving placebo (24.1%). In the [redacted] group, the most frequently reported Grade 3 local reaction after any dose was injection site pain (1.1%). Solicited systemic reactions were more common in participants receiving [redacted] (94.0%) than in those receiving placebo (63.5%), with 26.8% and 3.0%, respectively, reporting Grade 3 systemic reactions. In the [redacted] group, the most frequently reported Grade 3 systemic reactions after any dose were fatigue (13.4%), chills (11.0%) and headache (10.9%) (Kremsner 2021).

No safety concerns related to [redacted] were identified following administration of 2 doses of 12 µg [redacted] given 28 days apart, to a large population of participants at least 18 years old.

3.3.2 Dose Escalation

Escalation to the next higher dose cohort for each age group will be supported by clinical safety data from a minimum of 10 adults in the same age group who received the previous dose level. The decision to escalate will be based on review by the SRT as described in Section 3.1.1.

3.3.3 Maximum Planned Dose

The maximum planned dose of CV0501 is 200 µg in the present study. The rationale for evaluating doses up to 200 µg is based on the following considerations:

- **The optimal booster dose of CV0501 necessary to confer protection against COVID-19 disease caused by the Omicron variant (B.1.1.529) is unknown**. The Omicron variant contains at least 30 amino acid substitutions, 15 of which are in the receptor-binding domain (CDC 2021a). Accumulating evidence suggests that the Omicron variant can evade the immune protection conferred by vaccines and natural

infection (Section 1.1). Based on limited data, convalescent sera and antibodies from persons vaccinated with the mRNA COVID-19 vaccines manufactured by [redacted] were less effective at neutralizing the Omicron variant compared to WT virus (Section 1.1). Taken together, these data suggest that it is likely that higher doses could be necessary to generate adequate immunity to confer protection against the Omicron variant.

The range of doses to be tested as a booster dose in this Phase 1 dose escalation study in adults, 3 µg to 200 µg, brackets the 30 µg booster dose authorized by the FDA under EUA for the [redacted] the 50 µg booster dose authorized by the FDA under EUA for the [redacted] and the 100 µg primary vaccination dose for the [redacted]

Taken together, these data support the evaluation of a range of doses to determine the optimal safe and immunogenic dose to be evaluated further.

- **The optimal dose of CV0501 that could confer cross-protection against non-Omicron variants is unknown.** As the COVID-19 pandemic progresses, new SARS-CoV-2 variants are likely to emerge. Cross-protection against SARS-CoV-2 variants not contained in the vaccine may become important. For this reason, adequate dose-finding is necessary in Phase 1 to help determine the optimal dose that can safely induce high titers that could confer cross-neutralizing activity against new and emerging variants of concern.

3.3.4 Low Dose Evaluation

If the 12 µg dose level is demonstrated to be immunogenic, the immunogenicity and safety of lower dose levels (3 µg and 6 µg) of CV0501 will be evaluated. The scientific rationale for testing these additional lower dose levels is to evaluate whether CV0501 mRNA platform could be optimized for the development of multivalent vaccine(s).

4 Participant Selection and Withdrawal Criteria

4.1 Selection of Study Participants

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the eligibility criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

A participant must meet all 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
3. Has received at least 2 doses of CCI [redacted], with the last dose of vaccine received at least 6 months prior to screening
4. Negative for SARS-CoV-2 infection by RT-PCR test at screening
5. Is a male or nonpregnant female ≥18 years old
6. If the participant is a WOCBP, agrees to use at least 1 highly effective form of contraception for at least 30 days prior to the study vaccination up to 3 months after study vaccination.
7. Agrees to refrain from blood or plasma donation from the first study vaccination through end of study.
8. Has a body mass index of 18 to 40 kg/m^2, inclusive, at screening.
9. Is healthy or medically stable as determined by investigator judgment based on medical history, clinical laboratory tests, vital sign measurements, and physical examination findings

4.1.2 Exclusion Criteria

An individual who meets any of the following criteria will not be enrolled in the study:

1. Participant is female and has a positive pregnancy test result at screening.
2. Participant is female and is breastfeeding or will (re)start breastfeeding from the study vaccination to 3 months after vaccination.
3. Has an acute febrile illness with temperature ≥38.0°C or ≥100.4°F within 72 hours before study vaccination. Individuals with suspected COVID-19 symptoms should be excluded and referred for medical care.
4. Has a history of documented SARS-CoV-2 infection or COVID-19 within 6 months before screening.
5. Has a documented medical history of HIV, hepatitis B or hepatitis C infection prior to screening, or a positive test for these conditions at screening.
6. 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). 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 immunotherapy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or other similar or toxic drugs within 6 months of the first study vaccination. Inclusion of persons who use low dose topical, ophthalmic, inhaled, or intranasal steroid preparations is permitted.
7. 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.

8. Has a new onset, clinically significant, abnormal biochemistry or hematology finding (defined as ≥Grade 1) at screening (adults with Grade 1 laboratory abnormalities that have been stable for at least 6 months before enrollment may be included in the study).
9. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), Takayasu arteritis, granulomatosis with polyangiitis, psoriasis, and insulin-dependent diabetes mellitus (Type 1).
10. Has an unstable chronic medical condition. This refers to a condition requiring a new medication or increase in dose of current medication(s) or a condition requiring hospitalization within 6 months prior to screening.
11. Has a history of hypersensitivity or severe allergic reaction, including anaphylaxis, generalized urticaria, angioedema, and other significant reactions, to vaccines or to any component of the investigational product.
12. Has received or plans to receive any licensed vaccine within 4 weeks before or 4 weeks 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. Has had known close contact with anyone who had a confirmed SARS-CoV-2 infection within 2 weeks before study vaccination. Rescreening of these participants permitted after quarantine period is complete.
14. Has participated or plans to participate in another investigational study involving any investigational product or device within 6 months or 5 half-lives, whichever is longer, before the study vaccination through end of study.
15. Has received or plans to receive immunoglobulins or any blood or blood products within 3 months before the first study vaccination through end of study.

16. Has a bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
17. Has a history of alcohol abuse or other recreational drug use (excluding cannabis) within 6 months before study vaccination.
18. Has any abnormal skin condition or permanent body art (eg, tattoo) that would interfere with the ability to observe local reactions at the injection site.
19. Has a medical disease or psychiatric condition that, in the opinion of the investigator, precludes study participation because it would place the individual at an unacceptable risk of injury, render the individual unable to meet the requirements of the protocol, or interfere with the individual's successful completion of the trial.
20. Participant is an employee or family member of the investigator or study site personnel.

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

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

Individual participants may withdraw from the study at any time at their own request for any reason without prejudice to their future medical care by the investigator or at the study site. The reasons for participants withdrawing from the study will be recorded in the eCRF.

Participants will be informed of any new authorized or licensed booster vaccines that become available for prevention of 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:

- Participant request.
- Investigator request.
- The participant is noncompliant with the protocol.

- The participant has a serious or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study.
- The participant is lost to follow-up.
- Death.
- The sponsor terminates the study.

If a participant withdraws or is withdrawn from the study, ET procedures should be completed as indicated in the SOE (Table 13-1). Every effort will be made to continue to monitor the safety of participants who received a dose of IP and are withdrawn from the study.

4.2.1 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.

4.2.2 Replacements

Participants who withdraw may be replaced at the discretion of the sponsor after consultation with the SRT. Participants who are assigned to a group in error and not vaccinated may be replaced. Participants who withdraw for reasons connected to the study vaccine (eg, safety concerns after study vaccination) will not be replaced.

If the investigator believes there is a reasonable justification to do so, all screening procedures may be repeated (maximum 1 rescreening per individual is allowed). Only results from the rescreening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The participant can only be vaccinated once the investigator receives the results and confirms the eligibility criteria.

5 Study Vaccines

5.1 Method of Assigning Participants to Study Vaccine Groups

Participants in Part A will be assigned sequentially to a dose-level cohort by age group (Section 3.1). Participants in Part B will be randomly assigned on Day 1 to receive study vaccine by dose-level cohort.

Interactive response technology will be used to administer the randomization schedule. Biostatistics will generate the randomization schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IRT, which will link sequential participant randomization 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 randomization is complete for consistency in each participant's study records.

5.2 Study Vaccine Administration

Participants will receive 1 dose of IP on Day 1, in accordance with the study's SOE (Table 13-1). The volume to be administered will vary by dose level over a potential range of 0.3 mL to 0.7 mL; full details are described in the Pharmacy Manual.

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. The needle length recommendations for adults (by sex and weight) receiving an intramuscular injection in the deltoid muscle are as follows (CDC 2022b):

- Men and women, < 70 kg (152 lb): 25 mm (1 inch)
- Men, 70-118 kg (152-260 lb); Women, 70-90 kg (152-200 lb): 25-38 mm (1-1.5 inches)
- Men, > 118 kg (260 lb); Women, > 90 kg (200 lb): 38 mm (1.5 inches)

Standard vaccination practices must be observed, and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of IP should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. Details of IP administration will be recorded in the eCRF.

Refer to the Pharmacy Manual for additional instructions on study vaccine administration.

5.3 Identity of Investigational Product

Investigational product in this Phase 1 study refers to the CV0501 vaccine, which is a formulation of CCI [redacted]. that will be administered during the study.

CCI [redacted]

The IP information is presented in Table 5-1.

Table 5-1 Investigational Product Information

Intervention Name	**CV0501**
Type	Vaccine
Dose Formulation	Modified mRNA
Unit Dose Strength(s)	CCI [redacted] µg mRNA/mL
Dosage Level(s)	3, 6, 12, 25, 50, 75, 100, 150, 200 µg
Route of Administration	Intramuscular injection
Diluent	0.9% sodium chloride
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by GSK Biologicals SA or [redacted] CCI

Packaging and Labeling	IP will be provided in a glass vial as a sterile colloidal dispersion in a frozen liquid formulation as open-label supply. Each vial will be labeled as required per country requirement.

Diluent (0.9% sodium chloride solution for injection) will be provided centrally by PPD in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement.

Refer to the Pharmacy Manual for instructions on how to prepare and dispense the IP. Appropriately qualified and experienced study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist), as allowed by local, state, and institutional guidance, should prepare and dispense IP. A second staff member will verify the dispensing.

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.

In addition, PPD will provide the following participant supplies to study sites: eDiary devices, rulers, thermometers, and informational cards describing solicited symptoms and symptoms of COVID-19.

5.5 Overdose Management

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

There is no specific treatment recommended for an overdose.

Any overdose must be promptly reported to 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. Refer the participant to a higher level of care as clinically indicated.
3. Document the quantity of the excess dose in the eCRF.

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

5.6 Blinding

Allocation of participants to vaccine groups will proceed as described in Section 5.1. 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.

In this open-label study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. Study and site personnel, including the investigator, study staff and participants will be unblinded.

Preliminary reviews of available safety and immunogenicity data may be performed on an ongoing basis in an unblinded fashion. A statistical and programming team will perform 2 planned interim analyses during the study (Section 7.7). Unblinded safety summaries will be provided to the SRT to inform study decisions for progressing enrollment between groups (Section 3.1.1).

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 Therapies

5.8.1 Prior and Concomitant Therapy

Use of all prior and concomitant medications and vaccinations within 6 months of screening will be recorded in the participant's eCRF.

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

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.

Participants during this Phase 1 study will be allowed to receive a booster dose of a licensed or authorized COVID-19 vaccine, per national recommendations, if received at 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 as clinically indicated.

5.9 Study Holding Rules

The medical monitor, investigator, and SRT will continuously assess AEs against study holding rules (Table 5-2).

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	Necrosis at the injection site	≥1
1d	Confirmed or suspect myocarditis or pericarditis events not clearly attributable to any cause other than study vaccine	≥2
2a	Any same or similar Grade 3 related unsolicited events*, including but not limited to the identical MedDRA high-level term	≥2
2b	Same Grade 3 solicited local or systemic AE in an investigational group	≥3

* Includes laboratory abnormalities of clinical relevance, symptomatic or not, as determined by the investigator.

Study holding rules 1a, 1b, and 1c will be assessed by the investigators on a continuous basis. Study holding rules will lead to a hold of the vaccination in the entire study. Study holding rules 1d, 2a and 2b will be assessed by the SRT on an ongoing basis. A triggered study holding rule will lead to a hold of vaccination in the entire study.

If the sponsor confirms that a stopping rule has been met, the following actions will be taken:

1. The SRT (Section 11.1) will review all available safety data whenever any of the study holding rules are met. The SRT will recommend to the sponsor whether a cohort or group should be permanently stopped, modified, or continued unchanged. Medical judgment, considering all available safety data at the time of review, should be the basis for a recommendation to continue the study or not.

2. The stopping rule will pause enrollment and study intervention administration for all dose levels and age groups.

3. For all vaccinated participants, all other routine study activities, including ongoing data entry, reporting of AEs, participant reactogenicity eDiary completion, blood sample collection and participant follow-up will continue during the pause.

4. 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, including educating participants on the symptoms and means of reporting suspected myocarditis or pericarditis, are provided in Section 9.3. Study assessments will be performed in an outpatient setting at qualified study sites.

Refer to the SOE Table 13-1 for the full list of visits and assessments. Due to the ongoing pandemic, safety follow-up may be completed via televisits, as permitted by country regulations.

6.1 Safety Assessments

Safety will be assessed through the collection and evaluation of solicited and unsolicited AEs (Section 6.1.1.1.1), MAAEs (Section 6.1.1.1.1), SAEs (Section 6.1.1.1.2), and AESIs (Section 6.1.1.1.4). Safety will also be assessed by physical examinations, vital sign measurements, and clinical safety laboratory assessments.

All suspected cases of COVID-19 in study participants will be diagnosed and clinically evaluated, which may require unscheduled study site visits and additional SARS-CoV-2 laboratory testing (Section 6.1.2). Participant COVID-19 diagnosis and clinical evaluation may be performed by an outside medical provider following local standard of care.

All suspected or confirmed cases of myocarditis or pericarditis will be diagnosed and clinically evaluated (Section 6.1.3).

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 recorded by participants in an eDiary from Day 1 through Day 7 in response to specific questions (Section 6.1.1.5). After study vaccination all participants will be instructed to record local and systemic solicited AE symptoms in an eDiary. Local solicited AEs will include injection site pain, redness, and swelling and lymphadenopathy (localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the vaccination arm). Systemic solicited AEs will include fever, fatigue, headache, chills, myalgia, and arthralgia. 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 starting more than 7 days after vaccination will be captured as unsolicited AEs.

An unsolicited AE is defined as any AE that is volunteered from the participant. Unsolicited AEs will be monitored for 28 days after vaccination.

An MAAE is defined as an AE that results in a visit to a medical professional (eg, telemedicine visits, physician's office visits, urgent care visits, emergency room visits, or hospitalization).

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 an important medical event that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, jeopardizes the participant or may require medical or surgical intervention to prevent one of the other 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. All events of myocarditis and pericarditis will be considered important medical events and SAEs (Section 6.1.3).

6.1.1.1.3 Suspected Unexpected Serious Adverse Reactions

A SUSAR is defined as a serious 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, prespecified AESIs will include the following events:

- Virologically confirmed COVID-19 (see Section 6.4 for definition)
- Potential immune-mediated disorders (Section 13.4)
- Anaphylaxis or severe hypersensitivity within 24 hours after study vaccine administration
- Myocarditis
- Pericarditis

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 Intensity

The intensity, or severity, 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 or requires repeated use of non-narcotic pain reliever
	3	Severe: Prevents daily activity or requires use of narcotic pain reliever
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 the definition of an SAE (Section 6.1.1.1.2).

Refer to Section 6.1.2 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 Requirements for Serious Adverse Events and Adverse Events of Special Interest

Any AE that meets the definition of an SAE (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.

Cases of myocarditis or pericarditis (as defined in Section 6.1.3) occurring in temporal association with vaccination of study participants within 4 weeks after vaccination will be reported as SUSARs, as required by 21 CFR 312.32.

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 stable, or the participant is lost to follow-up.

6.1.1.5 eDiary

An eDiary will be used after study vaccination for participants to record solicited local injection site and systemic AEs during the 7 days after study vaccination for reactogenicity assessment. Study site personnel will instruct the participants on use of the eDiary. The site staff will review the eDiary data at Days 4 and 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 the definition of an SAE (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 SARS-CoV-2 Infection and COVID-19 Assessment and Definitions

Vaccine efficacy will not be evaluated in this study, but all laboratory-confirmed asymptomatic SARS-CoV-2 infections should be reported by the participant and documented as AEs, while virologically confirmed cases of COVID-19 are reported as AESIs (Section 6.1.1.1.4). Participant COVID-19 diagnosis and clinical evaluation may be performed by an outside medical provider following local standard of care. Any available isolate genotyping results will also be requested. Participants will be instructed to inform the investigator in the event of a positive SARS-CoV-2 diagnostic test. Serology testing for SARS-CoV-2 N protein will be performed prevaccination and postvaccination to monitor for undetected SARS-CoV-2 infections at the time points specified in the SOE (Table 13-1).

All participants with suspected COVID-19 may have an unscheduled visit for suspected COVID-19, as detailed in the SOE (Table 13-1). At this visit, participants will undergo the following assessments:

- Medical history
- SARS-CoV-2 RT-PCR (nasopharyngeal or mid-turbinate swab)
- Physical examination
- Vital sign measurements

- Review of adverse events
- Concomitant medication/vaccination

Participants with confirmed COVID-19 may have an unscheduled COVID-19 convalescent visit as detailed in the SOE (Table 13-1). 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. Alternatively, an investigator may utilize participant medical records from non-study care medical providers to verify whether a participant was infected with SARS-CoV-2.

Any 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:	Laboratory-confirmed SARS-CoV-2 N protein seroconversion without any of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea

COVID-19:	Virologically confirmed SARS-CoV-2 by RT-PCR with 1 or more of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea
Severe COVID-19:	Virologically confirmed SARS-CoV-2 infection with any 1 of the following: • Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg) • Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO) • Evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors) • Significant acute renal, hepatic, or neurologic dysfunction • Admission to a hospital or an intensive care unit • Death

6.1.3 Myocarditis and Pericarditis Assessment and Definitions

All suspected or confirmed cases of myocarditis or pericarditis will be diagnosed and clinically evaluated.

Participants reporting acute chest pain, shortness of breath, or other symptoms of myocarditis or pericarditis within 4 weeks after vaccination must be evaluated by a cardiologist with evaluation and management following current practice guidelines (eg, American Heart Association or local standard of care). Functional cardiac evaluation (eg, stress test echocardiogram) to detect potential late onset of cardiac function impairment must also be performed. Suspected myocarditis includes (but is not necessarily limited to) the following:

- New ECG abnormality that a cardiologist judges consistent with probable or possible myocarditis or pericarditis, including the following:

- Sustained atrial or ventricular arrhythmias
- Second degree Mobitz Type II or worse atrioventricular block, new bundle branch block
- Diffuse ST-segment elevation or PR-segment depression, compatible with pericarditis

- An abnormal troponin I value that is confirmed abnormal on repeat testing

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

6.1.3.1 Surveillance for Asymptomatic Myocarditis and Pericarditis

At the Day 8 visit, all participants will be assessed by 12-lead ECG for evidence of asymptomatic myocarditis or pericarditis, based on evidence that rare cases of myocarditis or pericarditis have occurred most frequently within 7 days of vaccination (CDC 2022a). All participants will also have a 12-lead ECG examination at screening to provide a baseline for comparison.

Asymptomatic acute myocarditis/pericarditis is defined as electrocardiographic changes suggestive of acute myocardial injury occurring in an asymptomatic participant within 4 weeks after administration of a COVID-19 mRNA vaccine, if other causes of acute cardiac disease are excluded. Electrocardiogram changes suggestive of acute myocardial injury and consistent with probable or possible myocarditis or pericarditis would include sustained atrial or ventricular arrhythmias, second degree Mobitz Type II or worse atrioventricular block, new bundle branch block, or diffuse ST-segment elevation or PR-segment depression. If any of these ECG changes are detected at the surveillance ECG occurring at the Day 8 visit, the findings will be reviewed by a cardiologist. If a diagnosis of myocarditis or pericarditis is confirmed, then the subject will be further evaluated and receive cardiology consultation, including cardiac enzyme assessment, echocardiography, or other assessments deemed clinically warranted by the treating clinician.

6.1.4 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:	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total and direct bilirubin, blood urea nitrogen, and creatinine
SARS-CoV-2:	• SARS-CoV-2 N protein serology (Ab) prevaccination and postvaccination to monitor for asymptomatic SARS-CoV-2 infections • SARS-CoV-2 RT-PCR (nasopharyngeal or mid-turbinate swab)
HIV/HBV/HCV	• Hepatitis B surface antigen test • HIV 4th generation antigen/Ab test • Anti-HCV Ab test (and RNA test if anti-HCV Ab positive)
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 per Appendix 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 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 and graded with the AE intensity grading scale (Section 6.1.1.2.1).

All laboratory tests with values considered clinically significantly and abnormal during participation in the study should be evaluated for the etiology and 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 sponsor should be notified.

All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual. If laboratory values from non-protocol-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.

A maximum of 120 mL of blood will be collected per participant per visit. This may include 50 mL of blood collected at 3 visits for participants in Part A enrolled at sites [redacted] The maximum amount of blood collected over the 6-month duration of the study is approximately 500 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

6.1.5 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.

6.1.6 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, oxygen saturation by pulse oximetry, respiration rate, systolic and diastolic blood pressure. 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.

6.2 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 Assessment of Immune Responses

Humoral and cellular immunogenicity assessments will be performed at sponsor-designated laboratories as detailed in the Study Manual. Blood samples will be collected at the time points indicated in the SOE (Table 13-1).

CCI [redacted]

CCI [redacted]

6.3.1 Assessment of Humoral Immune Responses

CCI [redacted]

6.3.2 Assessment of Cellular Immune Responses

CCI [redacted]

6.4 Genetics

Human genetics will not be assessed in this study.

7 Statistical 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.

7.1 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, 5 dose-level cohorts (Cohorts 1 to 5) each comprising 2 age groups. Cohorts 6 and 7 will comprise 1 age group (younger adults). 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. The sample size in Cohorts 6 and 7 is based on clinical feasibility rather than on statistical rationale. With 15 participants in each cohort, there is a 79.4% probability to observe at least one AE if the true incidence rate is 10%.

7.3 Analysis Sets

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

- Enrolled Set: All eligible participants who gave informed consent, regardless of the participants' treatment status in the study.
- Safety Set: All participants who receive 1 dose of IP. The Safety Set will be used for all analyses of safety. Data are analyzed according to treatment received. The Safety Set will be used for safety analyses.

- Per Protocol Immunogenicity Set: The PPI Set includes all eligible participants who received a dose of study IP per protocol and who have values for predose and Day 15 neutralizing Ab titers against pseudovirus bearing S protein from the Omicron variant of SARS-CoV-2. 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, laboratory-confirmed SARS-CoV-2 infections or immunosuppressive or immunodeficient conditions) or after a prohibited concomitant medication/vaccination (COVID-19 vaccination) will be excluded from the PPI Set. The analysis will be done according to the dose that participants received at Visit 1. The PPI Set will be used for the immunogenicity analyses.

7.4 Description of Subgroups to Be Analyzed

Subgroup analyses 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

All analyses will be performed by treatment group, combining the younger and older adult participants together, unless specified otherwise. 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).

7.5.2 Analysis of the Primary Safety Endpoints

The primary safety endpoints as detailed in Section 2 will be analyzed as described in the SAP. Laboratory abnormalities will be graded for severity following the FDA toxicity grading table (Section 13.5). For all safety endpoints, descriptive summary statistics will be provided for the Safety Set. Safety data listings will also be provided.

Refer to Section 13.3 for details on Bayesian logistic regression used during the safety monitoring of the study.

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. In addition to descriptive statistics for continuous variables (Section 7.5.1), confidence intervals and interquartile ranges will also be provided for continuous immunogenicity variables.

Seroresponse rate with 95% CI, GMT of specific Ab with corresponding 95% CI at each timepoint and GMI from baseline of specific Ab with corresponding 95% CI at each postbaseline timepoint over pre-injection baseline will be provided by 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

There are 2 planned interim analyses of safety and immunogenicity data for at least neutralizing Ab titers against SARS-CoV-2 WT, Omicron, and Delta variant pseudoviruses. The first interim analysis will be performed after all participants in Cohorts 1, 2, and 3 have completed the Day 15 study visit. The second interim analysis will be performed after all participants in Cohorts 4 and 5 have completed the Day 15 study visit. Details of these interim analyses will be described in the SAP.

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 course of 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. As part of the consent process, participants will be provided with educational materials describing the symptoms of myocarditis and pericarditis and guidance on contacting study personnel and seeking medical care if any of these symptoms occur. 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, a contract research organization (PPD, part of Thermo Fisher Scientific), and third party vendors.

11.1 Safety Review Team

The SRT will be an internal team, with representatives from both GSK and [redacted]. The role of the SRT in deciding dose escalation is described in Section 3.1.1. In addition, the SRT will review safety and immunogenicity data during the planned interim analyses and whenever any study holding rules are met (Section 5.9). The SRT may also recommend to permanently stop enrollment in a group. 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. The SRT will review interim analysis data.

Based on SRT review and recommendations, the sponsor may drop dose groups 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.

11.2 Monitoring

11.2.1 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.

11.2.2 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.

11.3 Management of Protocol Amendments and Deviations

11.3.1 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.

11.3.2 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.

11.4 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.

11.5 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.

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13 Appendices

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events

	Screening[a]	D1	D4	D8	D15	D29	D91	D181 (EOS)	ET Visit	Unscheduled Visit for Suspected COVID19	Unscheduled COVID-19 Convalescent Visit
Window	**D–14 to –1**	**0**	**±1**	**±1**	**±3**	**±3**	**±5**	**±7**	**NA**	**NA**	**NA**
Visit	**1**	**2**	**Phone**	**3**	**4**	**5**	**6**	**7**	**NA**	**NA**	**NA**
Informed consent	X										
Inclusion/exclusion	X										
Reassess study vaccine eligibility[b]		X									
Demographics	X										
Medical history (including vaccination history)	X										
Pregnancy test[c]	X	X									
CCI											
Physical examination[f]	X	X		X	X	X	X	X	X	X	X
Vital sign measurements[g]	X	X		X	X	X	X	X	X	X	X
Viral screening assays[h]	X										
Hematology and serum chemistry[h]	X	X[d]		X							
CCI											
Group assignment for Part A/ Randomization for Part B		X									
CCI											
Initiate eDiary for solicited AEs[i]		X									
12-lead ECG examination	X			X							
Site staff review of eDiary			X	X							
CCI											
COVID-19 assessment[k]										X[k]	X[k]

Note: Due to the ongoing pandemic, safety follow-up may be completed via televisits, as permitted by country regulations.

a. If the investigator believes there is a reasonable justification to do so, all screening procedures may be repeated (maximum 1 rescreening per participant is allowed). Only results from the rescreening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The participant can only be vaccinated once the investigator receives the results and confirms the eligibility criteria.

b. Prior to study vaccine administration, participants will be reassessed for development of any new condition that would be considered exclusionary including acute illness or pregnancy. Assessment will be based on pregnancy test results, participant-reported symptomology, vital sign measurements, and physical examination findings.

c. A serum pregnancy test will be performed at screening in WOCBP. A urine pregnancy test by dipstick will be performed prior to study vaccination. Negative confirmation is required prior to study vaccine administration. Pregnancy test may be repeated at an unscheduled visit per investigator's discretion.

d. On Day 1, the blood sample should be collected *before* study vaccine administration.

e. CCI [redacted]

f. 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.

g. 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 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.

h. Clinical safety laboratory testing will include hematology and serum chemistry. Screening laboratory tests may be repeated once for enrollment requirements. At unscheduled visits, clinical safety laboratory testing may be performed per investigator's discretion. Viral screening assays include HIV1/2 Antigen/Ab, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibodies (HCV Abs). Testing for HCV RNA will be performed in participants who test positive for HCV Ab.

i. An eDiary will be initiated for daily recording by the participant of solicited local and systemic adverse events.

j. Solicited local and systemic AEs will be collected during the 7 days after study vaccination via eDiaries. Unsolicited AEs will be collected for 28 days after study vaccination. SAEs, MAAEs, and AESIs will be collected for the duration of the study.

k. All suspected cases of COVID-19 in study participants will be diagnosed and clinically evaluated according to the definitions provided in Section 6.1.2. Such participants may have unscheduled study site visits and nasopharyngeal RT-PCR testing for SARS-CoV-2. An unscheduled visit may be performed for participants reporting symptoms consistent with COVID-19. An initial visit should be scheduled upon report of symptom onset, preferably within 3 days of symptom onset. Alternatively, an investigator may utilize participant medical records from non-study care medical providers to verify whether a participant was infected with SARS-CoV-2. An additional unscheduled,COVID-19 convalescent visit will be preferably conducted within the month after the participant is

confirmed with COVID-19. At the convalescent visit, the investigator will seek medical records documenting any treatments and hospitalizations related to COVID-19.

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 1 FSH measurement >40 IU/L (or mIU/mL) is required.

- Females on HRT and whose menopausal status is in doubt will be required to use 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 of learning 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.
- Any female participant who becomes pregnant while participating in the study will discontinue the IP.

13.3 Appendix 3: Bayesian Logistic Regression Model

A Bayesian logistic regression model will be used to determine posterior probabilities of unacceptable reactogenicity (Grade 3 solicited AEs) at the current or next dose level in Part A, as described below:

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

where

- p(d) represents the probability of having a Grade 3 event at dose d,
- logit(p) = ln(p/(1-p)),
- d* = 50 µg is the reference dose,
- α is an intercept parameter, reflecting the expected logit value at the 50 µg reference dose level,
- β_1 is a dose effect,
- β_2 is an age group effect.

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

1. 80% weight for $\alpha \approx$ normal (mean=-0.8473, var=1) and $\ln(\beta_1) \approx$ normal (mean=-0.0556, var=1), reflecting a rate of 30% at 50 µg, and 10% at 12 µg).
2. 20% weight for $\alpha \approx$ normal (mean=-0.4055, var=1) and $\ln(\beta_1) \approx$ normal (mean=0.10612, var=1), reflecting an intolerable dose (ie, a rate of 40% at 50 µg and 12% at 12 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 greater than 50% posterior probability that the rate at a current or next dose is greater than 30% will inform the SRT in their decision to continue at the current or next dose. This will be applied by each dose and age group.

Hypothetical scenarios for determining posterior probabilities based on combined younger age group and older age group data are presented in Table 13-2.

Table 13-2 Hypothetical Data Scenarios for Determining Posterior Probabilities

Scenario	Dose (µg)	#Events	#Participants	CD – P(OD)	Next Dose	ND – P(TD)	ND – P(OD)
1	12	0	30	0	25	0.984	0.016
	25	0	30	0	50	0.860	0.1442
	50	0	30	0	100	0.917	0.083
	100	0	30	0	200	0.984	0.016
	200	0	30	0	-	-	-
2	12	0	30	-	25	0.984	0.016
	25	4	30	0.01	50	0.633	0.367
	50	6	30	0.097	100	0.352	0.648*
	100	8	30	0.407	200	0.1717	0.829*
	200	15	30	0.992*	-	-	-

*Stopping rule met, ie, ND – P(OD) >0.5
CD = current dose; NA = not applicable; ND = next dose; P(TD) = probability of target dose; and P(OD) = probability of overdose.
In this evaluation, the age effect was not considered in the model.
When fitting the model, 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.
Rows in red should not be in the table, since the stopping rule would have been met at the previous dose; however, the rows are included for illustration purposes only.
NOTE: It should be noted that the Bayesian model may be applied in a small number of exposed participants since it will be applied at each SRT review.

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	

Medical Concept	Additional Notes
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	

Medical Concept	Additional Notes
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

Medical Concept	Additional Notes
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) 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	Includes the following: • Acute necrotizing myelitis

Medical Concept	Additional Notes
other inflammatory demyelinating variants	• 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

Medical Concept	Additional Notes
	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 lichen planopilaris

Medical Concept	Additional Notes
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"

Medical Concept	Additional Notes
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-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)"
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Löfgren syndrome
Susac's syndrome	

13.5 Appendix 5: Grading for Laboratory Abnormalities

Laboratory abnormalities will be graded for severity using the following FDA toxicity grading table (DHHS 2007). Clinically relevant laboratory abnormalities (Grades 1-3) will be reported as AEs. All Grade 4 laboratory abnormalities will be reported as SAEs.

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 phosphatase (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 x ULN	1.26 – 1.5 x ULN	1.51-1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal (increase by factor)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
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.

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, 23 Jun 2022

Rationale for Amendment 1:

The main purposes of Amendment 1 are to respond to requests from regulatory authorities, to correct a typographical error in the wording of the primary safety endpoint, and to 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 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, grammatical, and formatting corrections are not included in this summary table.

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
Section 1.2 (Risk:Benefit Considerations) Section 6 (Study Assessments and Procedures) Section 9.3 (Participant Information and eConsent)	Added language describing increased education and guidance to participants regarding myocarditis and pericarditis	Response to FDA request for increased risk mitigation for myocarditis and pericarditis
Section 2 (Study Objectives and Endpoints)	Corrected the primary safety endpoint to read: Percentage of participants with abnormal laboratory findings drawn 8 days after study vaccination	To correct a typographical error in the number of days

Section Number and Name	Description of Change	Brief Rationale
Section 3 (Study Design) Section 13.1 (Appendix 1: Schedule of Events)	Increased the length of the screening period from 7 to 14 days, resulting in an increased study duration per participant from 187 to 194 days	To allow investigators more time to assess eligibility of participants and enhance study management
Section 3 (Study Design) Section 6.1 (Safety Assessments) Section 6.1.2 (SARS-CoV-2 Infection and COVID-19 Assessment and Definitions) Section 13.1 (Appendix 1: Schedule of Events, footnote k)	Clarified that participants will be asked to report any positive SARS-CoV-2 diagnostic test results and that investigators may verify SARS-CoV-2 infection from records of an outside medical provider	To improve surveillance for SARS-CoV-2 infections during the study and to expedite infected participant access to medical care while limiting their travel and resulting exposure to the general population while infected
Section 4.1.1 (Inclusion Criteria)	In criterion 8, increased the upper limit of body mass index from 32 to 40 kg/m^2	To broaden eligibility to better reflect the target patient population without expected increased risk to participants
Section 4.1.2 (Exclusion Criteria)	In criterion 12, removed the phrase, "including a COVID-19 vaccine"	Response to Australian regulatory authority request to clarify criterion 12. The inclusion criteria and Section 5.8.2 of the protocol adequately describe the allowed intervals between COVID-19 vaccination and vaccination with IP
Section 5.2 (Study Vaccine Administration)	Inserted recommendations for needle length by sex and weight	To address revision of inclusion criterion 8, included guidance on recommended needle length
Section 5.9 (Study Holding Rules)	Timing windows for study holding rules 1c and 2a were eliminated, and a new study holding rule for myocarditis or pericarditis (1d) was established	Response to FDA request to widen the scope of study holding rules
Section 6.1 (Safety Assessments) Section 6.1.3 (Myocarditis and Pericarditis Assessment and Definitions)	Added specifications for diagnosing and evaluating cases of suspected or confirmed myocarditis or pericarditis	Response to FDA request for increased risk mitigation for myocarditis and pericarditis

Section Number and Name	Description of Change	Brief Rationale
Section 6.1.1.1.2 (Serious Adverse Events)	Clarified that all events of myocarditis and pericarditis will be considered important medical events and SAEs	Response to FDA request for increased risk mitigation for myocarditis and pericarditis
Section 6.1.1.3.2 (Reporting Suspected Unexpected Serious Adverse Reactions)	Added that cases of myocarditis or pericarditis occurring in temporal association with vaccination of study participants within 4 weeks after vaccination will be reported as SUSARs, as required by 21 CFR 312.32	Response to FDA request for increased risk mitigation for myocarditis and pericarditis
Section 6.1.3.1 (Surveillance for Asymptomatic Myocarditis and Pericarditis) Section 13.1 (Appendix 1: Schedule of Events)	Added a 12-lead ECG examination to the assessments conducted at the Day 8 visit, with cardiologist follow-up if findings of myocarditis or pericarditis are suspected or confirmed	To enhance surveillance for asymptomatic myocarditis and pericarditis and respond to FDA request for increased risk mitigation for myocarditis and pericarditis
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